ウェブサイト公開用

（様式 10）
（海外特別研究員事業）

令和　2　年　3　月　31　日

海 外 特 別 研 究 員 最 終 報 告 書

独立行政法人 日本学術振興会 理事長　殿

採 用 年 度　平成 30 年度
受 付 番 号　201870034
氏　　名　中山 真紀子

（氏名は必ず自署すること）

海外特別研究員としての派遣期間を終了しましたので、下記のとおり報告いたします。
なお、下記及び別紙記載の内容については相違ありません。

記

1. 用務地（派遣先国名）用務地：ハーバード医科大学ボストン小児病院（国名：　米国　）

2. 研究課題名（和文）※研究課題名は申請時のものと違わないように記載すること。
新規遺伝子同定によるステロイド抵抗性ネフローゼ症候群でのポドサイト分子病態の解明

3. 派遣期間：平成　30　年　4　月　1　日　～　令和　2　年　3　月　31　日

4. 受入機関名及び部局名
Boston Children's Hospital, Harvard Medical School, Division of Nephroology, Hildebrandt Laboratory

5. 所期の目的の遂行状況及び成果…書式任意　**書式任意（A4 判相当 3 ページ以上、英語で記入も可）**
（研究・調査実施状況及びその成果の発表・関係学会への参加状況等）
（注）「6. 研究発表」以降については様式 10－別紙 1～4 に記入の上、併せて提出すること。

5. 所期の目的の遂行状況及び成果（研究・調査実施状況及びその成果の発表・関係学会への 参加状況等）

所期の目的の遂行状況及び成果（最終報告書）

採用年度 平成 30 年度
受付番号 201870034
氏 名 中山 真紀子

Whole Project Title: Discovering and characterizing novel genetic causes of nephrotic syndrome

Project 1: Identifying genes associated with Steroid resistant nephrotic syndrome (SRNS)

Project Summary
SRNS is a major factor leading to chronic renal failure in children and adolescents. The laboratory of the mentor has discovered 35 of the 50 genes known to cause monogenic SRNS (Lovric et al., NDT 2016). However about 70% of the disease causes are still unknown. Working as one of the lab members, I will aim to identify new causative monogenic and will elucidate the molecular pathology by using the whole exome sequencing (WES).
First year of the project was focused on SRNS accompanied with proteinuria and hematuria. We extended our gene panel of screening by incorporating gene associated with Alport syndrome (AS) and atypical hemolytic-uremic syndrome (aHUS). We detected pathogenic mutations in 18 of the 34 genes analyzed, leading to a molecular diagnosis in 14.1% of families (51 of 362). Disease-causing mutations were detected in 3 AS-causing genes in 17 families (4.7%), 3 aHUS-causing genes in 5 families (1.4%), and in 12 SRNS-causing genes in 29 families (8.0%). We observed a much higher mutation detection rate for monogenic forms of CKD in consanguineous families (35.7% vs. 10.1%).
We present the first estimate of relative frequency of inherited AS, aHUS (6.1%) versus SRNS (8.0%) in a typical pediatric cohort with proteinuria and hematuria. Important therapeutic and preventative measures may result from mutational detection in individuals with proteinuria and hematuria.

Background
Steroid Resistant Nephrotic Syndrome (SRNS), defined as a subgroup of nephrotic syndrome resistant to a standardized steroid therapy, is the second most leading cause of early onset end-stage kidney disease in children and adolescents in worldwide. SRNS often requires dialysis or renal transplantation for survival. Given the impact of patients with chronic renal failure and end-stage kidney failure on the medical economy, elucidating the pathogenesis of SRNS is an urgent issue to lead to find a potential treatment. With the progress of recent analysis technology, many causative genes involved in SRNS have been identified. The Hildebrandt Laboratory, where the applicant is currently working at and where this research would be conducted, has collected nearly 4,000 SRNS patients from medical research facilities around the world and has identified and characterized 35 genes out of 50 disease genes associated with SRNS. We were the first to show that in a high fraction of patients with SRNS (30%, 526/1,783) a causative monogenic mutation can be identified by exon sequencing in 30 known SRNS genes (Lovric et al., NDT 2016; Sadowski et al., JASN 2015). Recurrent identification of full penetrance single-gene causes of NS (e.g. podocin) has implicated the renal glomerular podocyte at the center of the pathogenesis. Establishing efficient methods for the functional assays in vitro for podocytes is of utmost importance to discover pathogenic genes of SRNS. Based upon the previous findings, Dr. Hildebrandt and his group has discovered that podocyte migration rate represents a cellular phenotype for the pathogenesis of SRNS (Gee et al., JCI 2013; Ashraf et al., JCI 2013). He and his colleages have established podocyte migration assay (PMA) to assess the podocyte function in vitro. Studying and working with the world-leading laboratory in SRNS genetics will allow not only to identify new responsible genes of SRNS but also to explore the possibility to elucidate patho-mechanism of SRNS through learning in-depth about the podocyte, which would be my own research theme.

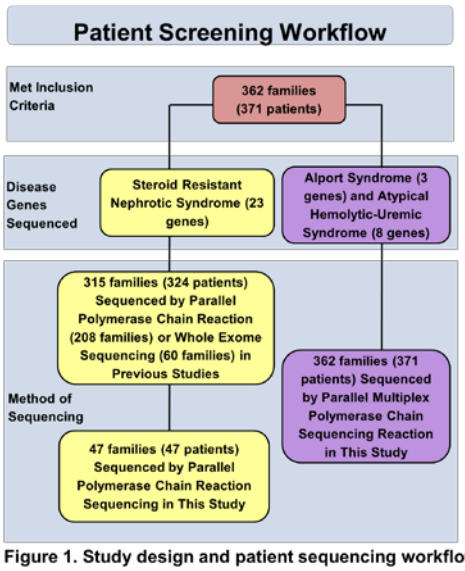


Figure 1. Study design and patient sequencing workflow.

Alport syndrome (AS) and atypical hemolytic-uremic syndrome (aHUS) are rare forms of chronic kidney disease (CKD) that can lead to a severe decline in renal function. In children and young adults, steroid resistant nephrotic syndrome (SRNS) is more common than AS and aHUS, causing 10% of childhood-onset CKD1, 2, 3. In recent years, multiple monogenic

causes of AS, aHUS and SRNS have been identified, but their relative prevalence has yet to be studied in a typical pediatric cohort of children with proteinuria and hematuria. We hypothesized that identification of causative mutations by whole exome sequencing in known monogenic nephritis and nephrosis genes would allow etiologically distinguishing nephritis from SRNS in a typical pediatric group of patients with both proteinuria and hematuria.

Method

With an established approach to identify candidate genes with WES, we aimed to identify genes associated with SRNS. conducted panel exon sequencing for 11 AS, aHUS and thrombocytopenic purpura-causing genes in an international cohort of 371 patients from 362 different families who presented with both proteinuria and hematuria before age 25 (**Table 1**). In parallel, we conducted either whole exome sequencing or panel exon sequencing for 23 SRNS-causing genes analysis in all patients (**Figure 1, 2**).

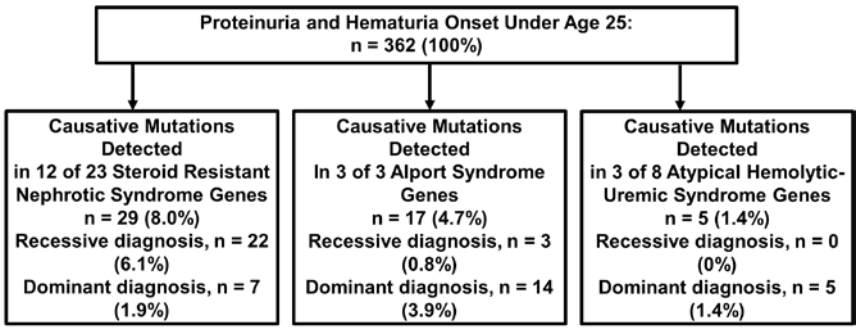


Figure 2. Solve rate for 362 families (371 patients) with proteinuria (>300 mg/day) and hematuria manifesting before age 25

Table 1. Genes included in the gene panel.

Alport Syndrome	
Gene synbol	inheritance
COL4A3	AR/AD
COL4A4	AR
COL4A5	XLD

Atypical Hemolytic-Uremic Syndrome	
Gene synbol	inheritance
ADAMTS13	AR/AD
C3	AR/AD
CD46	AR/AD
CFH	AR/AD
CFHR5	AD
CFI	AD
DGKE	AR
THBD	AD

Nephrotic Syndrome	
Gene synbol	inheritance
ACTN4	AD
ADCK4	AR
ARHGAP24	AD
ARHGDIA	AR
CD2AP	AR
COQ2	AR
COQ6	AR
CRB2	AR
CUBN	AR
INF2	AD
ITGA3	AR
ITGB4	AR
LAMB2	AR
LMX1B	AD
MYO1E	AR
NPHS1	AR
NPHS2	AR
PDSS2	AR
PLCE1	AR
PTPRO	AR
SMARCAL1	AR
TRPC6	AD
WT1	AD

Result

Mutation detection

In a pediatric cohort of 371 patients (362 families) who had proteinuria and hematuria with an onset before 25 years of age, we examined for mutations in 11 genes that are known monogenic causes of AS (3 genes), aHUS (7 genes) or TTP (1 gene) if mutated (Supplementary data, Table S1) and for 23 genes that are known as monogenic causes of SRNS (Supplementary data, Table S2). Consanguinity was present in 56 of the 362 families screened (15.5%). We detected mutations in three of the three AS-causing genes and in three of the seven aHUS-causing genes (Table 1). We did not detect any mutations in the TTP-causing gene ADAMTS13. We detected causative mutations in 12 of the 23 SRNS-causing genes (Table 1). Mutations that likely explained the molecular etiology of disease were detected 51 of 362 unrelated families (14.1%) (**Figure 3, 4**).

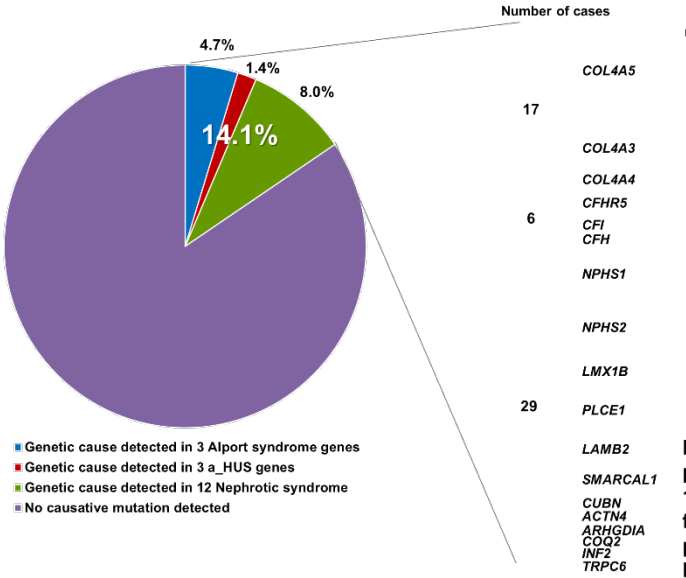
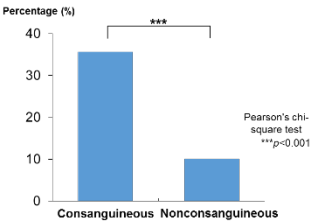


Figure 3. Distribution of pathogenic variants detected in 18 of 34 sequenced genes in 56 families presenting with proteinuria (>300 mg/day) and hematuria before age 25.



	Consanguineous	Nonconsanguineous
Cases	56	306
Mutation detected	20	31

Figure 4. Mutation detect rate in consanguineous and non-consanguineous cases.

Genes with pathogenic variants

Variants were validated as previously described in the methods and in Sadowski et al. [16]. Mutations were detected in three AS-causing genes in 17 families: COL4A5 (10 families), COL4A3 (6 families) and COL4A4 (1 family) (Tables 2 and 3). Mutations were detected in three aHUS-causing genes in five families: CFHR5 (three families), CFH (one family) and CFI (one family) (**Tables 2 and 3**).

Table 2. Genotype and phenotype of patients with pathogenic variants in 11 genes that if mutated, cause AS, aHUS or TTP.

Gene	Family	Ethnicity	Consan-guinity	Gender	Zygosity	p.change	PP2/MT/SHIFT	conser-ved to	gnomAD	Age of onset	Biopsy	Treatment (response)
COL4A5	A5192	Turk	Y	M	hemi	Splice	-32.2% /-0.4%/-11.1%	NA	0/2/2/178120 (2 hemi)	3 years	FSGS, TubAt	SR, CP(NR)
	A965	Euro	Y	M	hemi	p.Arg92_Gly93del	NA/NA/NA	*Dm*	-	15 years	AS,	SR, CS(CR)
	A3676	Indian	Y	M	hemi	Splice	-100%/-100% /-100%	NA	-	5 years	ND	SR
	A2917	Slavic	N	M	hemi	p.Gly406Val*68	NA/NA/NA	NA	-	2 years	Non-specified	-
	A3933_21	Indian	N	M	hemi	p.Gly545Asp	1/Del/DC	*Dm*	-	6 years	MCNS, MesP, TBM	-
	A3933_22	Indian	N	M	hemi	p.Gly545Asp	1/Del/DC	*Dm*	-	7 years	MCNS, MesP, TBM	-
	B711	Euro	N	M	hemi	p.Gly594Asp	0.355/Del/DC	*Dm*	-	15 years	AS, FSGS	SR
	A1963	Hisp	Y	M	hemi	p.Gly644Asp	1/Del/DC	*Dm*	-	14 years	NA	SR, CP(PR)
	B28	Arabic	Y	M	hemi	p.Glu1355Asn*22	NA/NA/NA	NA	-	1 year	NA	-
	A4926	Filipino	N	M	hemi	p.Gln1437Glu	0.407/Del/DC	*Dm*	1/3/19/197664 (3 hemi)	1 year	NA	ACEi
	A169_21	Turk	Y	M	hemi	p.Pro1480His*74	NA/NA/NA	NA	-	7 years	Cresscentic GN	SR, CP(NR)
	A169_22	Turk	Y	M	hemi	p.Pro1480His*74	NA/NA/NA	NA	-	1 year	Cresscentic GN	SR,TX
COL4A3	A2041	Euro	N	M	het	p.Gly91Asp	0.994/Del/DC	*Dr*	0/1/30960	18 months	FSGS	ACEi(UR)
					het	p.Leu1474Pro	1/Del/DC	*Dr*	0/735/276998			
	A1916	Slavic	N	F	het	Splice	-71%/-15.4% /-2.4%	NA	-	6 years	MPGN type 1	SS(PR), CS(NR), MMF(UR)
	A2490	Kazakh	N	F	het	Splice	+2.8%/+0.9% /+0.2%	NA	0/1/246078	9 years	ND	SS(CR)
	A1479	Turk	Y	F	het	p.Pro660Thr	0.661/Del/DC	*Gg*	0/5/277150	4 years	ND	SS(CR)
	A2358	Asian	Y	M	hom	p.Gly721Val*26	NA/NA/NA	NA	0/3/240254	10 years	FSGS	SR
	A2609	Euro	N	M	het	p.Arg1496Gln	0.989/Del/DC	*Gg*	0/11/276940	10 years	ND	SS(CR)
COL4A4	B789	Cauc	N	F	hom	splice	-100%/-100% /-100%	NA	-	4years	FSGS	-
CFHR5	A4967	African	N	M	het	p.Ser78Pro	0.986/Tol/PMP	NA	0/32/277182	7 years	Active SLN	SS(PR), ESRD
	A2351	Cauc	N	F	het	p.Glu163Arg*35	NA/NA/NA	NA	0/564/276160	14 years	Diffuse MesP, TBM	SR, CP(UR)
	A3422	Arabic	N	M	het	p.Phe539Val	0.998/Del/DC	NA	0/5/277086	4 years	MPGN	-
CFH	A4035	Euro	N	F	het	p.Pro503Ala	0.746/Del/PMP	*Ci*	0/4/245456	13 years	FSGS, TMA	SS(PR)
CFI	A2336	Asian	N	F	het	Splice	-21.2%/-11.9%/-12.3%	NA	19/2400/276954	9 years	ND	-

Cauc = caucasian, Ci = Ciona intestinalis, CP = cyclophosphamide, CR = complete response, CS = cyclosporine, DC = disease causing, Del = deleterious, Dm = Drosophila melanogaster, DMS = diffuse mesangial sclerosis, Dr = Danio rerio, Euro = European, F = female, FSGS = focal segmental glomerulosclerosis, Gg = Gallus gallus, GN = glomerulonephritis, Hemi = Hemizygous, Het = heterozygous, Hisp = hispanic, Hom = homozygous, M = male, MCNS = minimal change, nephrotic syndrome, MesP = mesangial proliferation, MMF = mycophenolate mofetil, MPGN = membrane proliferative glomerulonephritis, NA = not applicable, ND = not done, NR = no response, PMP = polymorphism, PR = partial resonse, SLN = sclerosing lobular nephritis, SR = steroid resistant, SS = steroid sensitive, TBM = thin basement membrane, TMA = thrombotic microangiopathy, Tol = tolerated, TubAt = tubular atrophy, Turk = Turkish, TX = transplant, UR = unknown response

In addition, mutations were detected in 12 SRNS-causing genes in 29 families: NPHS1 (5 families), NPHS2 (5 families), LMX1B (4 families), PLCE1 (4 families), LAMB2 (3 families), SMARCAL1 (2 families), ACTN4 (1 family), ARHGDIA (1 family), COQ2 (1 family), CUBN (1 family), INF2 (1 family) and TRPC6 (1 family) (Tables 4 and 5). No pathogenic variants were found in the following 16 genes: ADAMTS13, ADCK4, ARHGAP24, C3, CD2AP, CD46, COQ6, CRB2, DGKE, ITGA3, ITGB4, MYO1E, PDSS2, PTPRO, THBD and WT1. Of the 55 different disease-causing mutations detected in this study, 19 (34.5%) were novel variants that had never previously been reported in databases containing human disease-causing mutations.

Table 3. Genotype and phenotype of patients with pathogenic variants in 23 genes that cause nephrotic syndrome if mutated.

Gene	Family	Ethnicity	Consan-guinity	Gender	Zygosity	p.change	PP2/MT/SHIFT	conser-ved to	gnomAD	Age of onset	Biopsy	Treatment (response)
NPHS1	A1803	Cauc	N	M	hom	p.Ala47Pro*81	NA/NA/NA	NA	0/2/241678	<1 month	MCNS	CS(NR)
	A3775	Indian	N	F	het	Splice	-100%/0% /-100%	NA	0/1/245036	1 year	Diffuse MesP	SS(CR)
					het	p.Gly968Val	1/Del/DC	*Ce*	0/1/236378			
	A3380	Asian	N	M	het	p.Asp310Asn	0.99/Del/DC	*Dm*	0/3/241700	<1 month	ND	-
					het	Splice	-91.9% /-77.2%/-2.9%	NA	-			
	B115	Cauc	N	F	hom	p.Pro519Ser	0.984/Tol/PMC	*Dr*	-	<1 month	ND	-
	A1500	Afr-Am	N	F	hom	p.Ser910Pro	0.959/Del/DC	*Dr*	-	1 year	MCNS	-
NPHS2	A4681	Arabic	Y	F	hom	p.Met1*	NA/NA/NA	NA	-	7 years	GS	SR
	A4624	Arabic	Y	F	hom	p.Leu156Phe*11	NA/NA/NA	NA	-	1 year	MPGN	SR, CP(NR), CS(NR)
	B188	Hisp	Y	F	hom	p.Arg286Thr*17	NA/NA/NA	NA	0/18/275798	3 years	MCNS	TX
	A1616	Cauc	N	F	hom	p.Val290Met	0.998/Del/DC	*Dr*	0/33/276038	5 months	ND	-
	A2239	Turk	N	M	hom	p.Ala309Val	0.742/Del/DC	*Ce*	-	<18 years	GS	-
LMX1B	A200	Turk	Y	F	het	p.Arg246Gln	1/Del/DC	*Ce*	-	8 years	GS	SR, HD
	A2175	Euro	N	M	het	p.Arg246Gln	1/Del/DC	*Ce*	-	4 years	GS	SR, CS(PR)
	A3180	Euro	N	F	het	p.Arg246Gln	1/Del/DC	*Ce*	-	18 years	GS	ACEi(UR), HD, TX
	A4009	Arab	Y	F	het	p.Thr310Arg	0.701/Del/DC	*Gg*	-	<1 month	MCNS	SR, CS(NR)
PLCE1	A3233	Arabic	Y	F	hom	p.Arg1057*	NA/NA/NA	NA	0/1/245964	2 years	ND	SR, CP(NR)
	A3617	Arabic	Y	F	hom	p.Asn1127*	NA/NA/NA	NA	-	7 months	GS	-
	A3510	Turk	Y	F	hom	p.Lys1534Glu	0.998/Del/DC	*Sc*	-	1 year	ND	-
	A3869	Arabic	Y	M	hom	p.Lys1841Glu	1/Del/DC	*Sc*	-	7 months	GS	-
LAMB2	A1757_21	Hisp	N	M	hom	p.Thr48Ser	1/Del/DC	*Dr*	0/9/239510	13 years	GS	SR, MMF(NR)
	A1757_22	Hisp	N	F	hom	p.Thr48Ser	1/Del/DC	*Dr*	0/9/239510	13 years	GS	-
	A2356	Asian	Y	M	hom	p.Arg246Trp	1/Del/DC	*Ce*	0/0/17184	1 year	Finish type	-
	A1613	Euro	N	M	hom	Splice	-100%/0% /-100%	NA	0/1/109858	<1 month	Dilated tubules, Microcysts	-
SMARCAL1	A3146	Euro	N	F	het	p.Arg17*	NA/NA/NA	NA	0/2/246210	9 years	GS	-
					het	p.Phe279Ser	0.985/Tol/DC	*Ci*	0/23/277230			
	A4162	Euro	N	F	hom	p.Ser579*	NA/NA/NA	NA	-	4 years	GS	SR, CS(UR)
ACTN4	A1055	Kurd	Y	M	het	P.Arg536Ser	0.933/Del/DC	*Dr*	-	10 years	GS	SS(CR), CS(CR)
ARHGDIA	A1432	Jewish	Y	F	hom	p.Gly173Val	1/Del/DC	*Sc*	0/1/246016	2 years	DMS	CS(NR), TX
	A1432	Jewish	Y	M	hom	p.Gly173Val	1/Del/DC	*Sc*	0/1/246016	1 year	ND	TX
COQ2	A103	Euro	N	F	het	p.Asn228Ser	0.918/Tol/DC	*Ce*	0/32/276228	1 year	GS	SR, CS(PR)
					het	p.Leu286Phe	0.997/Del/DC	*Dm*	0/2/245656			
CUBN	A1213_21	Balkan	N	M	hom	p.Asp872Leu*3	NA/NA/NA	NA	0/6/276980	8 years	ND	-
	A1213_22	Balkan	N	M	hom	p.Asp872Leu*4	NA/NA/NA	NA	0/6/276980	5 years	ND	-
	A1213_23	Balkan	N	M	hom	p.Asp872Leu*5	NA/NA/NA	NA	0/6/276980	1 month	ND	-
INF2	A675	Euro	N	F	het	p.Ala13Thr	0.982/Tol/DC	*Dr*	1/85/240928	16 years	GS	Steroid(UR)
TRPC6	A4685	Arabic	N	F	het	p.Arg175Trp	1/Del/DC	*Dr*	-	17 years	GS	CS(NR)

Conclusion

We present the first estimate of relative frequency of inherited AS, aHUS (6.1%) versus SRNS (8.0%) in a typical pediatric cohort with proteinuria and hematuria. Important therapeutic and preventative measures may result from mutational detection in individuals with proteinuria and hematuria.

Project 2: ADCK4 deficiency destabilizes the coenzyme Q complex

Project Summary

ADCK4 mutations generally manifest as steroid-resistant nephrotic syndrome, and cause coenzyme Q_{10} (CoQ_{10}) deficiency. However, the function of ADCK4 remains obscure. We, therefore, investigated ADCK4 function using mouse and cell models. Podocyte-specific *Adck4* deletion in mice significantly reduced survival and caused severe focal segmental glomerular sclerosis, which were prevented by treatment with 2,4-dihydroxybenzoic acid (2,4-diHB), a CoQ_{10} precursor analog. ADCK4 knockout podocytes exhibited significantly decreased CoQ_{10} level and defects in mitochondrial function, which were rescued by 2,4-diHB treatment, thus attributing these phenotypes to decreased CoQ_{10} levels. Moreover, ADCK4 interacted with mitochondrial proteins including COQ5, while ADCK4 knockout decreased COQ complex levels. These findings reveal the function of ADCK4 and a treatment strategy for nephrotic syndrome caused by *ADCK4* mutations.

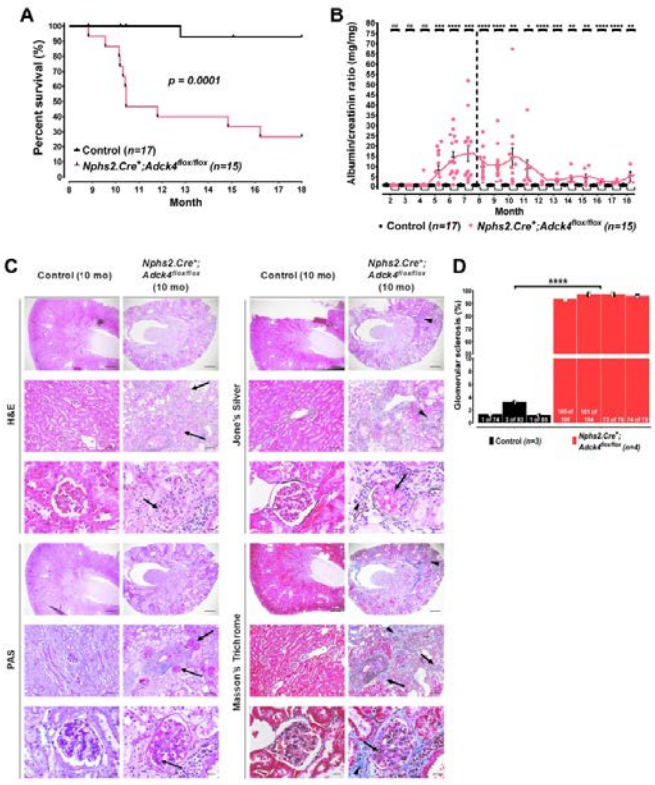


Figure 5. *Nphs2.Cre+;Adck4flox/flox* mice developed focal segmental glomerulosclerosis.

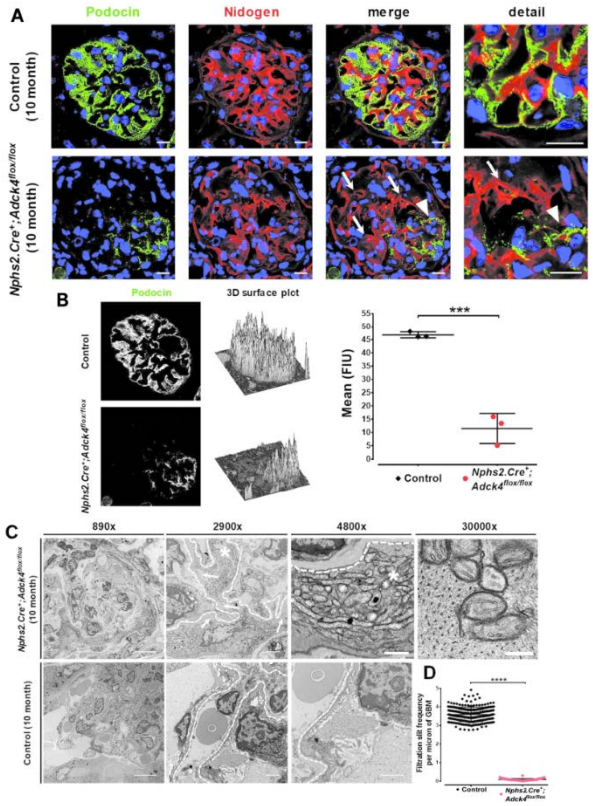


Figure 6. *Nphs2.Cre+;Adck4flox/flox* mice exhibited glomerulopathy.

Background

Primary CoQ deficiencies due to mutations in ubiquinone biosynthetic genes (*COQ2*, *COQ4*, *COQ6*, *COQ7*, *COQ9*, *PDSS1*, *PDSS2*, *ADCK3*, and *ADCK4*) have been identified. Clinical manifestations of CoQ_{10} deficiency vary depending on the genes involved, and mutations in the same gene can result in diverse phenotypes depending on the mutated allele. *COQ2*, *COQ6*, *PDSS2*, and *ADCK4* have also been implicated in steroid-resistant nephrotic syndrome (SRNS). Although no effective therapy has been described for SRNS, supplementation of CoQ_{10} in cases of SRNS resulting from CoQ_{10} deficiency acts to alleviate the associated clinical symptoms. This is partially true for ADCK4-related glomerulopathy, and several cases have been reported accordingly. However, it is not clear whether ADCK4 functions in a manner similar to that of ADCK3. Mutations in the *ADCK4* (aarF domain containing kinase 4, also known as *COQ8B*) gene generally manifest as adolescence-onset SRNS, sometimes accompanied with medullary nephrocalcinosis or extrarenal symptoms, including

seizures. The molecular mechanisms underlying SRNS resulting from *ADCK4* mutations are not well understood, largely because the function of ADCK4 is unclear. Therefore, in the current study, we investigated the function of ADCK4 using mouse and cell models.

Method

To elucidate the function of ADCK4 in podocytes, we examined a podocytespecific *Adck4* knockout mouse model and ADCK4-knockout podocytes. The $Adck4_{podKO}$ mice and ADCK4-knockout podocytes were then treated with 2,4- dihydroxybenzoic acid (2,4-diHB), a CoQ_{10} precursor analog, or with a vehicle only. Proteomic mass spectrometry analysis was also performed to further elucidate the function of ADCK4.

Result

Abrogation of *Adck4* in mouse podocytes caused focal segmental glomerulosclerosis and albuminuria (**Figure 5**). *In vitro* studies revealed that, in ADCK4-knockout podocytes, CoQ_{10} concentration, respiratory chain activity, and mitochondrial potential were all significantly reduced, while a subsequent increase in the number of dysmorphic mitochondria was observed (**Figure 6**). However, treatment of 3-month-old $Adck4_{podKO}$ mice or ADCK4-knockout cells with 2,4-diHB served to prevent the development of renal dysfunction and reversed mitochondrial dysfunction in podocytes (**Figure 7**). Moreover, ADCK4 interacted with mitochondrial proteins including COQ5 as well as cytoplasmic proteins including myosin and heat shock proteins (**Figure 8**). Thus, ADCK4 knockout decreased the COQ complex level, while the COQ5 level was rescued following overexpression of ADCK4 in ADCK4-knockout podocytes.

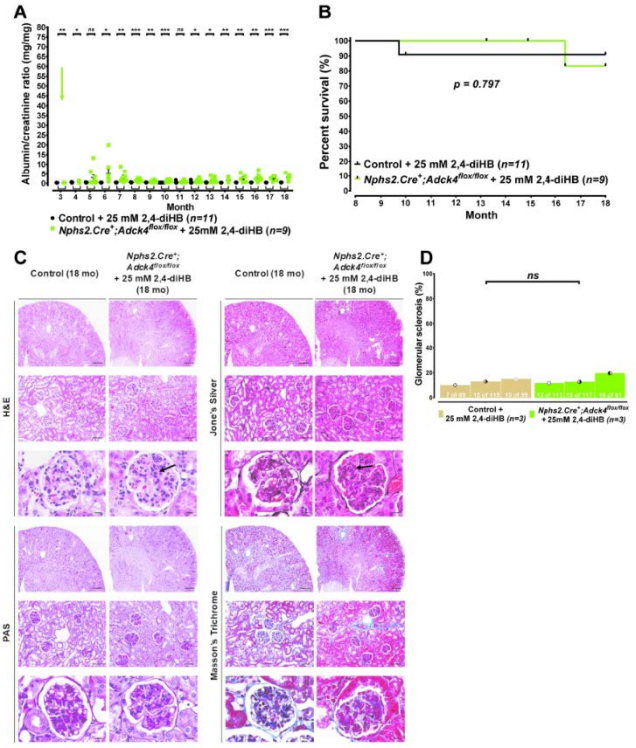


Figure 7. Treatment of *Nphs2.Cre+;Adck4flox/flox* mutant mice with 2,4-diHB prevented FSGS progression, resulting in normal survival rate.

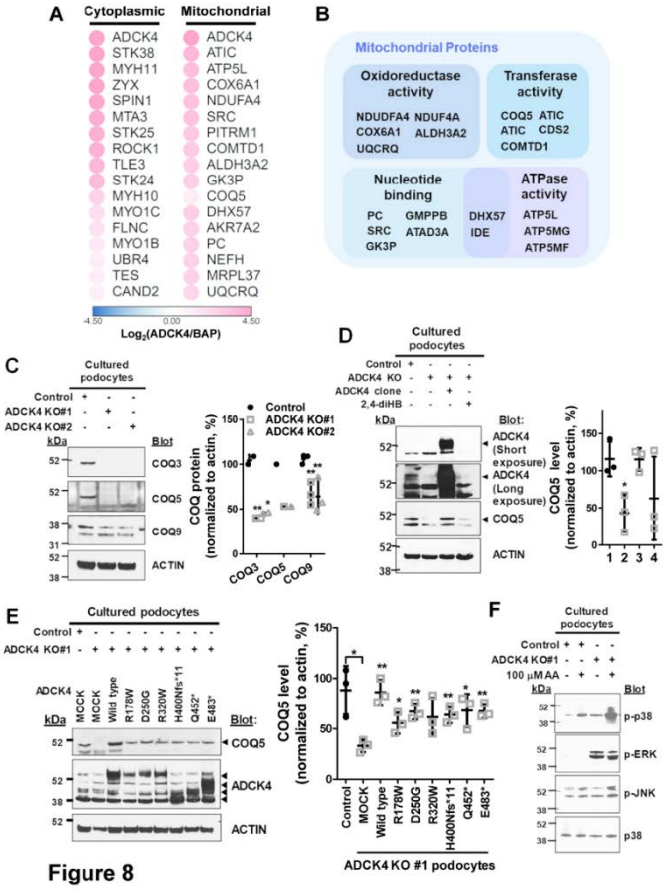


Figure 8

Figure 8. ADCK4 interacted with COQ5 and stabilized complex Q in podocytes.

Conclusion

ADCK4 is required for CoQ_{10} biosynthesis and mitochondrial function in podocytes. Our study also suggests a potential treatment strategy for nephrotic syndrome resulting from *ADCK4* mutations.