Treatment of Focal Segmental Glomerulosclerosis

Hong Kong 2015.12.13

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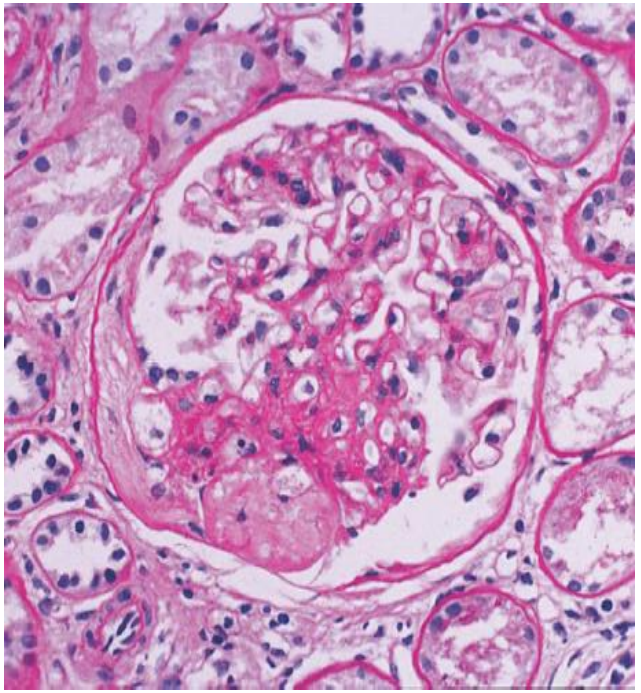
1 Overview

2 Pathogenesis

3 Diagnosis and Treatment

Focal Segmental Glomerulosclerosis

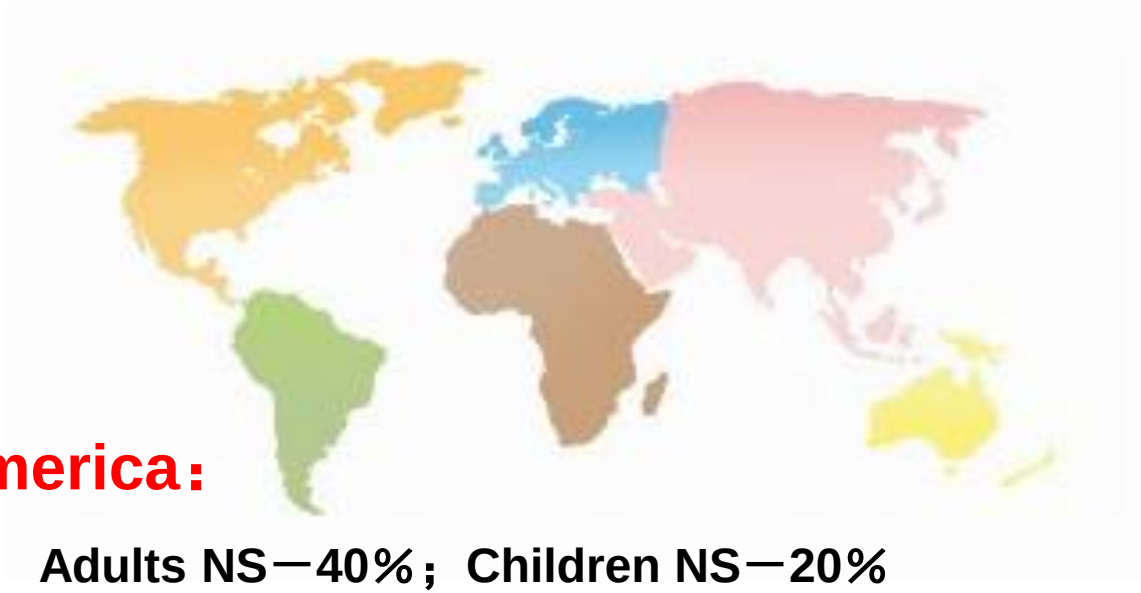
- First described in 1957 by Rich
- Accounting for 10%~ 30% of all renal biopsies
- Incidence has been increasing recently
- Typical manifestations：
  - ✓ Obvious proteinuria
  - ✓ Hypertension
  - ✓ worsening renal insufficiency
- One of the common causes of ESRD



Semin Nephrol 2006 ,26(2): 89 -94

Nephrol Dial Transplant 2009, 24: 870-876

The Epidemiology of FSGS（Global）



- **America：**
  - **Adults NS－40%；Children NS－20%**
  - **Incidence of FSGS-ESRD : 7 pmp**
  - **Renal biopsies：**

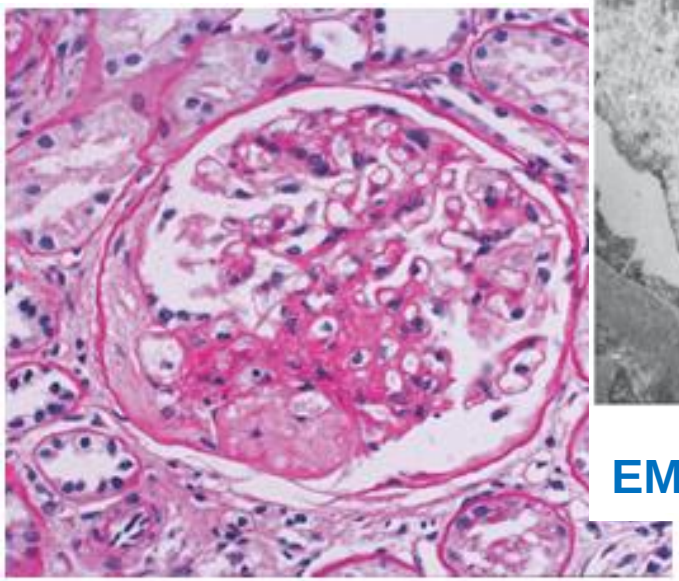
    12.2% (Haas M, 1995)-18.7% (D'Agati, 1994)
- **South Korea：**
  - **Renal biopsies： 5.9% (1997-2001)**

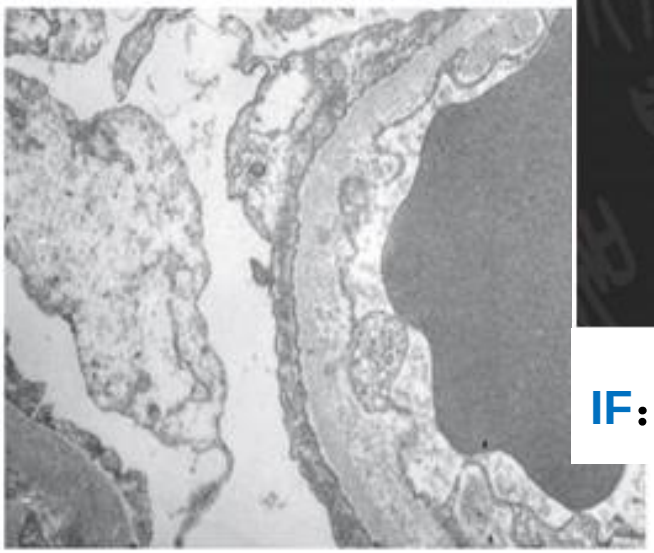
The Epidemiology of FSGS (China)

- **China：**
  - **Peking University First Hospital ：3.3%(1998-2002)，3.8%(2003-2007)**
  - **Nanjing General Hospital：6.4%(1979-1989)，5.2%(1990-1999)**
  - **Ruijin Hospital：16.7%(2003-2005)，18.5%(2006-2008)**

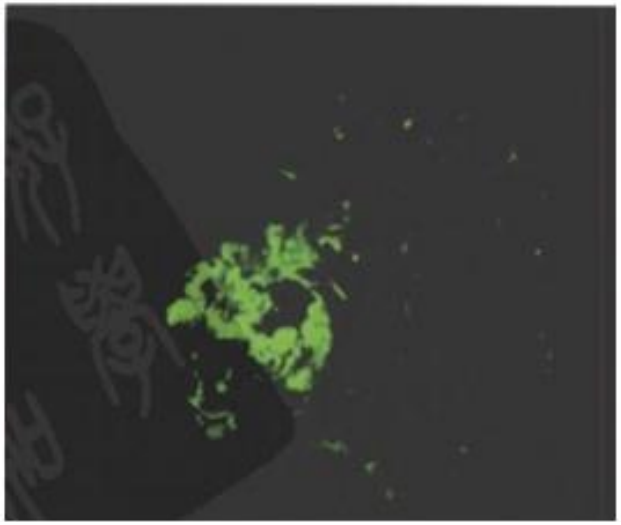
Xie J, Chen N. Contrib Nephrol. 2013;181:1-11.

Pathological Feature





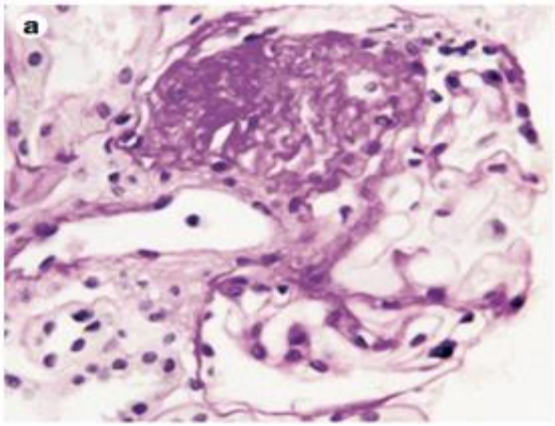
EM：foot-process effacement



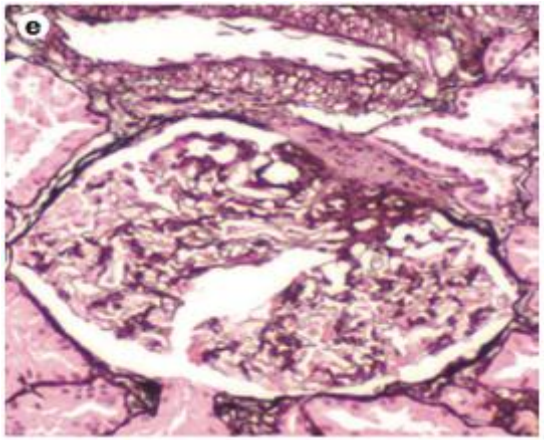
IF：deposits of IgM and C3

LM： Focal Segmental Glomerulosclerosis

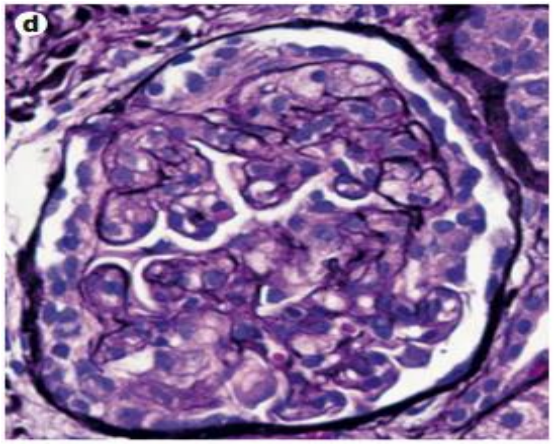
Pathologic Classification



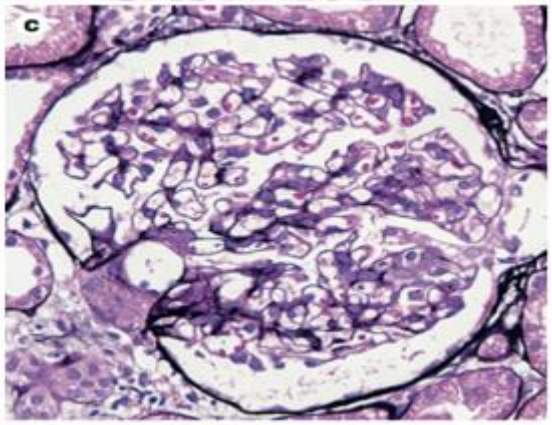
NOS



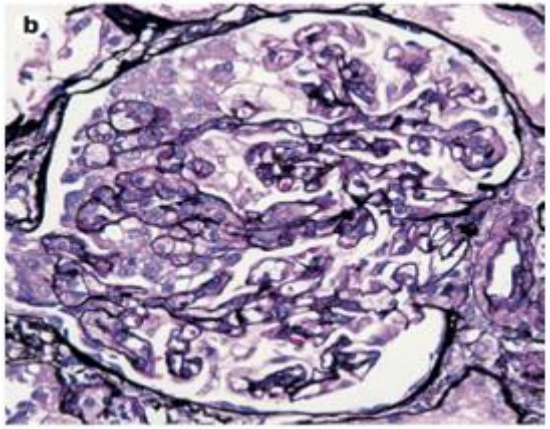
Hilar



Cellular



Tip



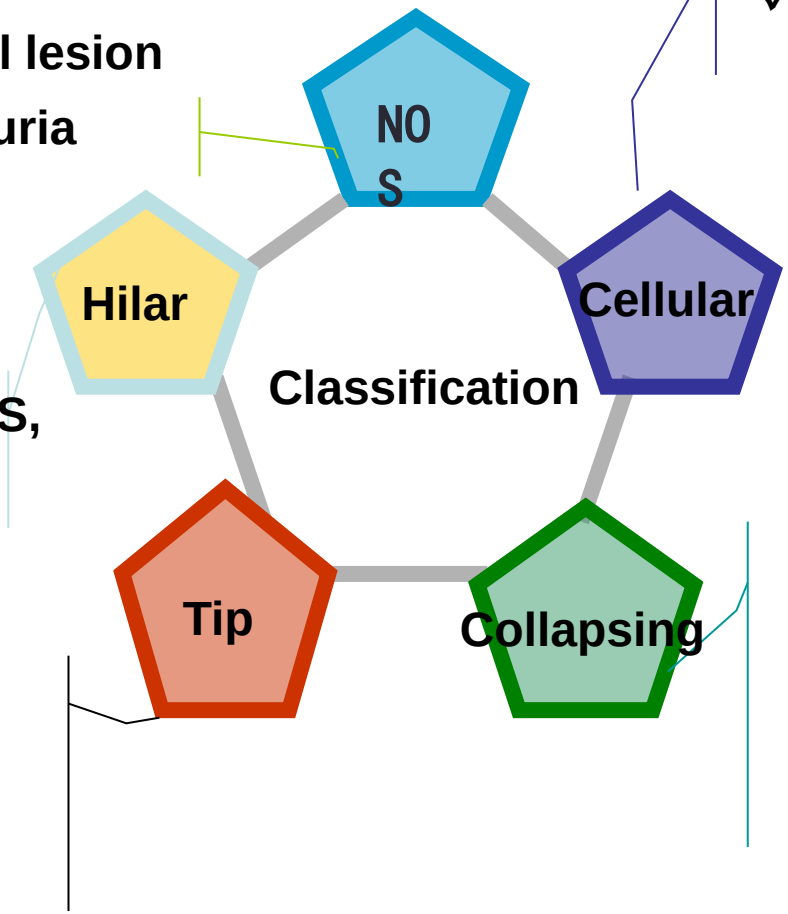
Collapsing

Fogo, A. B. *Nat. Rev. Nephrol*; doi:10.1038/nrneph.2014.216

Characteristics & Outcomes

- ✓ Most common
- ✓ Tubulointerstitial lesion
- ✓ Massive proteinuria

- ✓ Accidental onset



- ✓ Also in secondary FSGS, DM、obesity etc.

- ✓ Best prognosis
- ✓ Steroid-sensitive NS

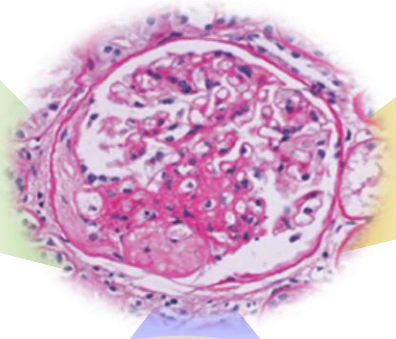
- ✓ Poorest prognosis
- ✓ Frequent in African Americans
- ✓ Poor response to steroid

Clin J Am Soc Nephrol. 2013 Mar;8(3):399-406.

Etiology Classification

Primary FSGS

Unknown



Secondary FSGS

obesity、 reflux nephropathy 、drugs、infections

……

Familial FSGS

Mutations of podocyte related molecules

Ren Fail. 2003; 25: 759-764
Kidney Int. 1996; 50: 1582-1590
Nat Med. 2011; 17: 952-960
Pediatr Nephrol. 2004; 19: 1075-1092

1 Overview

2 Pathogenesis

3 Diagnosis and Treatment

Pathogenesis mechanism

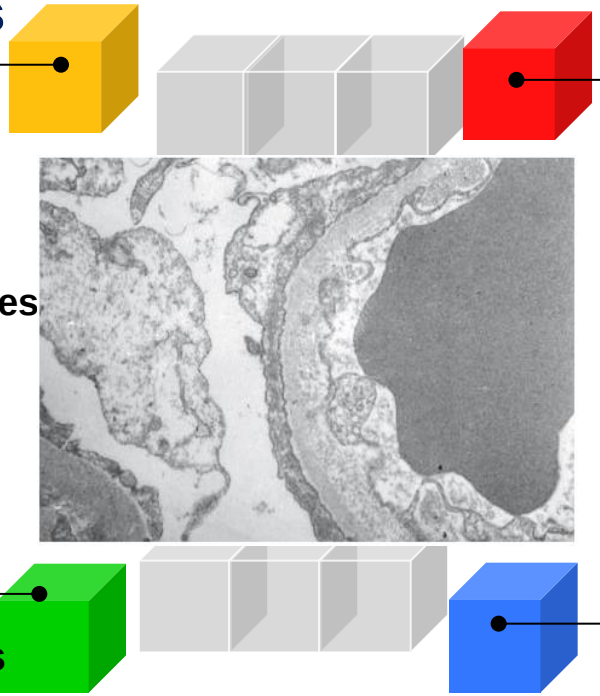
Permeability factors

Circulating factor

- suPAR
- IL-13

Podocyte-associated molecules

- Angptl4
- Integrinβ 3



toxicity

- Viral infection、drugs、heavy metal, etc.
- Collapsing is common

hemodynamics

- Decreased nephron mass
- Low birth weight
- Vessel dilation
- Hillar type is common

heredity

- Podocyte genes mutations
- Other genes mutations

Reviewed in Parikh, AJKD 59: 336, 2012

Familial FSGS genetic mechanism

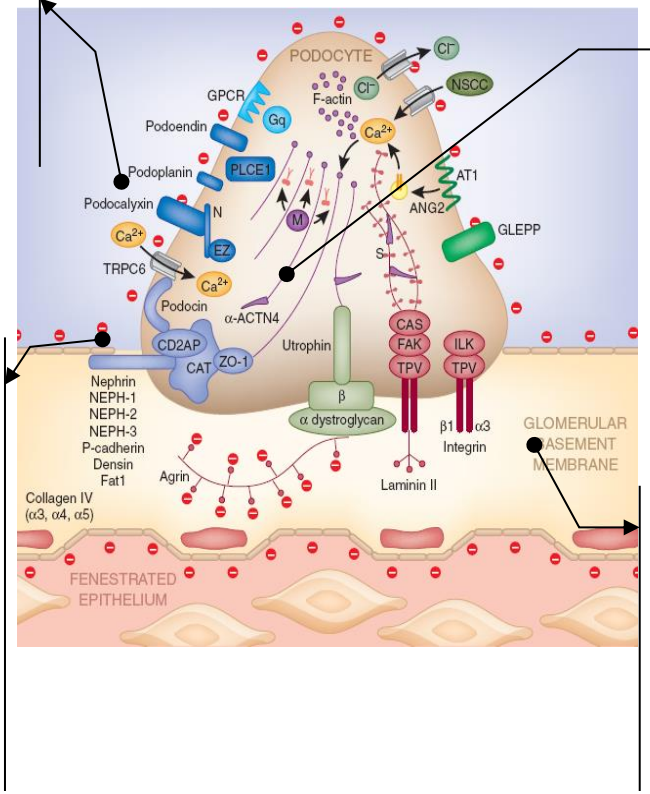
Pathogentic genes of FSGS

Membrane ionic channel

- *TRPC6* (adults)

Slit Diaphragm

- *NPHS1* (children)
- *NPHS2* (children, adults)
- *CD2AP* (children)



Cytoskeleton

- *ACTN4* (adults)
- *INF2* (adults)

Transcription Factors

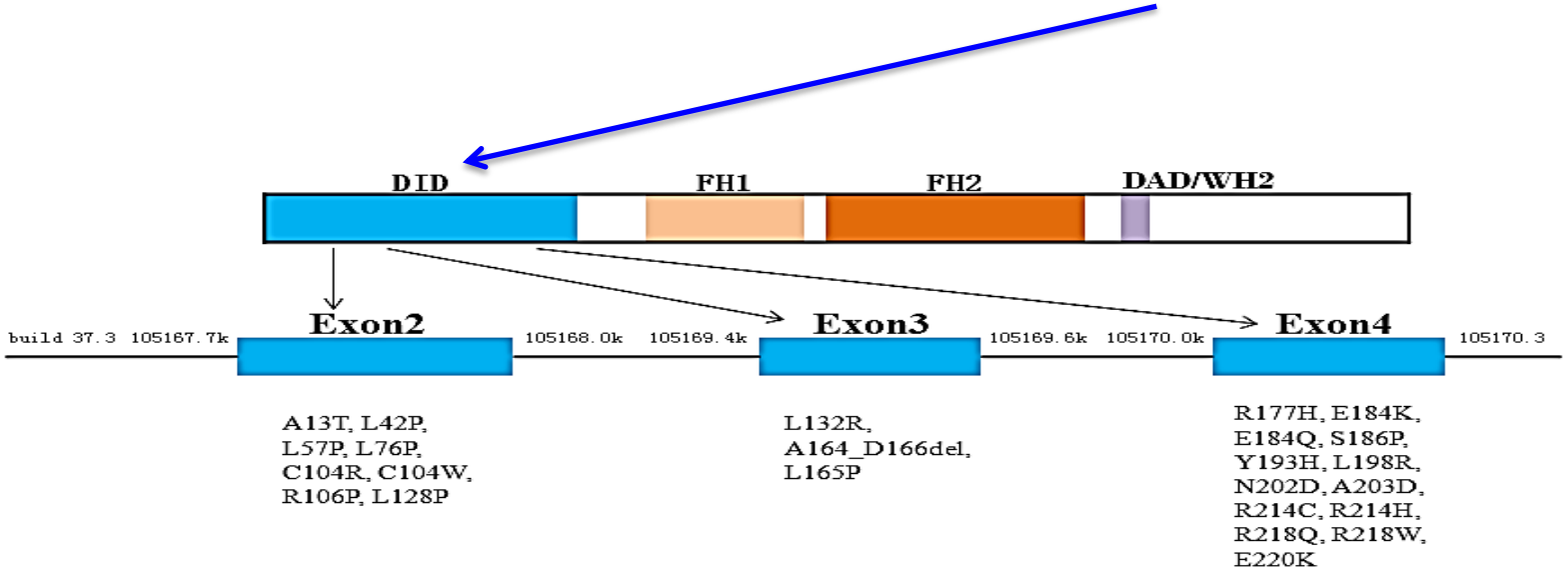
- *WT1* (children)
- *PAX2* (children)
- *Lmx1b* (children)

Kestila M Molecular Cell.1998(1):575-582
Nat Genet. 2000 Apr;24(4):349-54.
Science. 2005 Jun 17;308(5729):1801-4

Putaala H. Hum Mol Genet 10:1-8
Nat Genet. 2000 Mar;24(3):251-6
Nat Genet. 2010 Jan;42(1):72-6. Epub 2009

Podocyte cytoskeleton protein—INF2

- **Location:14q32**
- **Encoding forming nucleation factor － actin-regulating proteins**
- **Mutations cause adult-onset FSGS（2010）**
- **Mutation rate：9.8%-17%（most common in Caucasian）**
- **Pathogenic mutations mainly locate in DID domain**



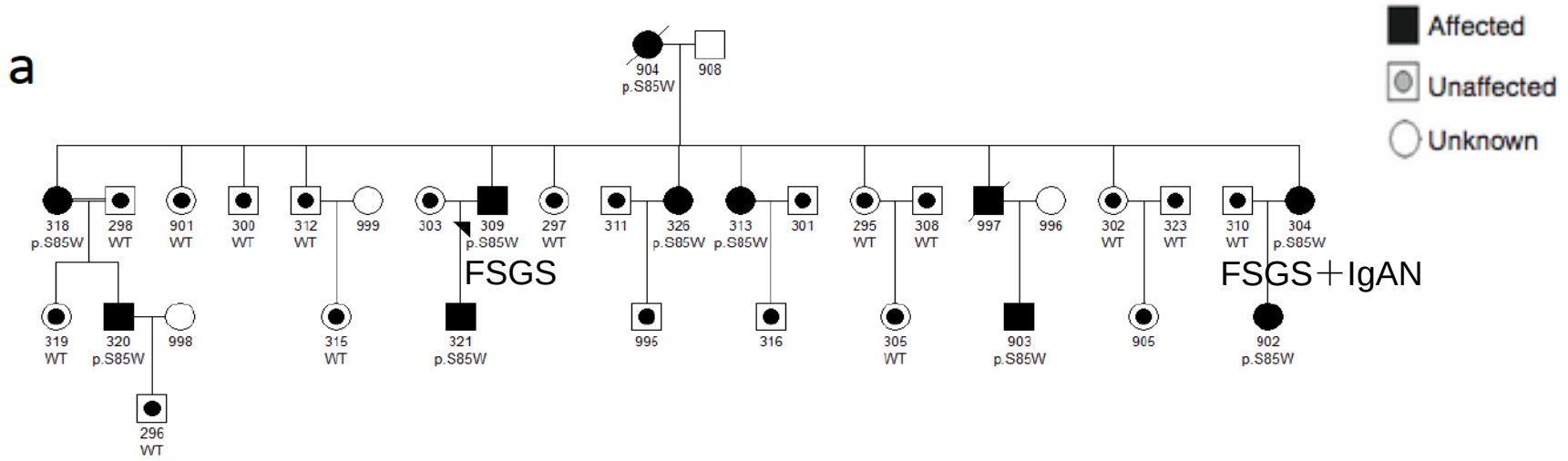
Nat Genet. 2010 Jan;42(1):72-6. Epub 2009
J Am Soc Nephrol 22: 239–245, 2011

Proc Natl Acad Sci U S A. 2011 Feb 15;108(7):2933-8
Kidney Int. 2012 Jan;81(1):94-9

Family FSGS research 1
—linkage analysis and precise mapping

Novel mutations in the *inverted formin 2* gene of Chinese families contribute to focal segmental glomerulosclerosis

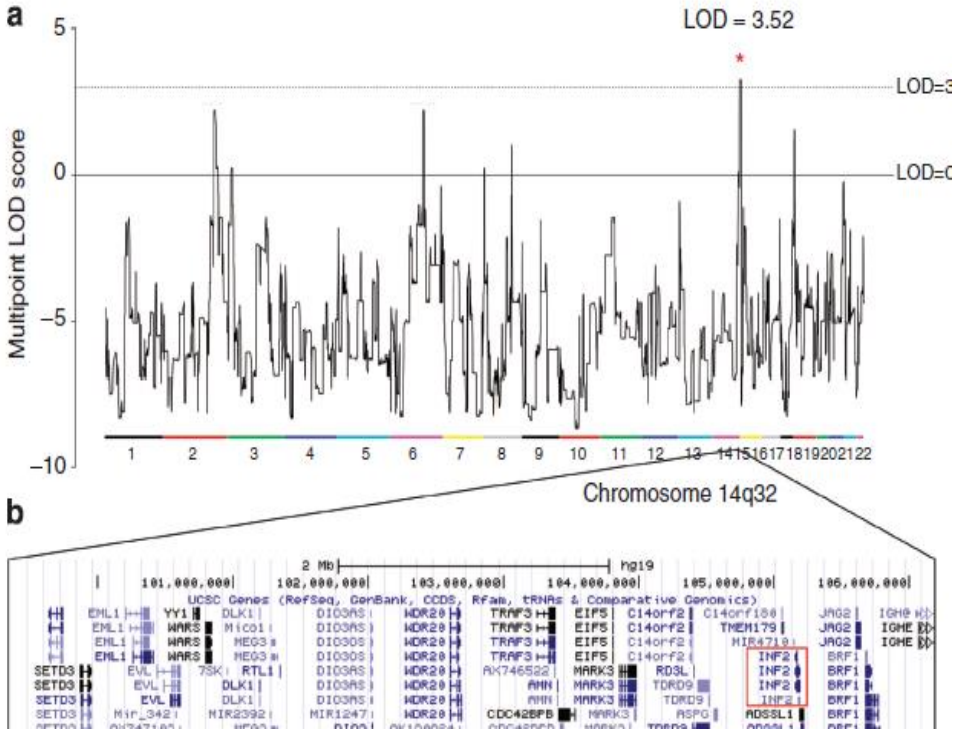
Jingyuan Xie[1,6], Xu Hao[1,6], Evren U. Azeloglu[2], Hong Ren[1], Zhaohui Wang[1], Jun Ma[1], Jian Liu[1], Xiaodan Ma[3], Weiming Wang[1], Xiaoxia Pan[1], Wen Zhang[1], Fang Zhong[1], Yifu Li[4], Guoyu Meng[3], Krzysztof Kiryluk[4], John Cijiang He[5], Ali G. Gharavi[4] and Nan Chen[1]

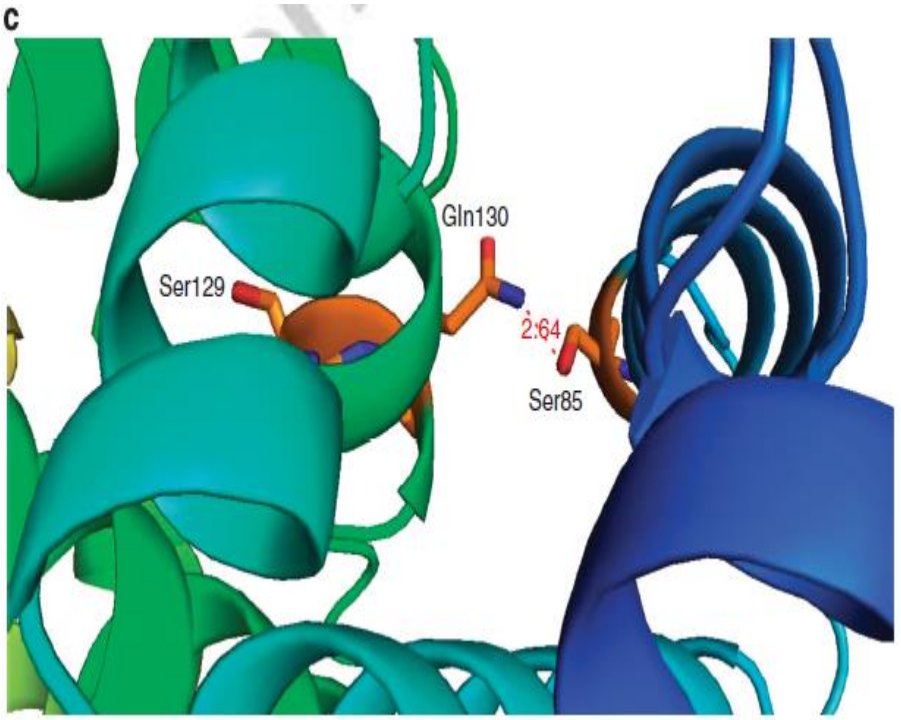


- **Autosomal Dominant**
- **55 adult-onset FSGS families，34 IgAN families**
- **The largest pedigree including 100 family members, 11 affected individuals**
- **Onset age:20~60, massive proteinuria and ESRD**

Xie J, Hao X, …., Chen N. Kiidney international 2015

Linkage analysis and structure prediction





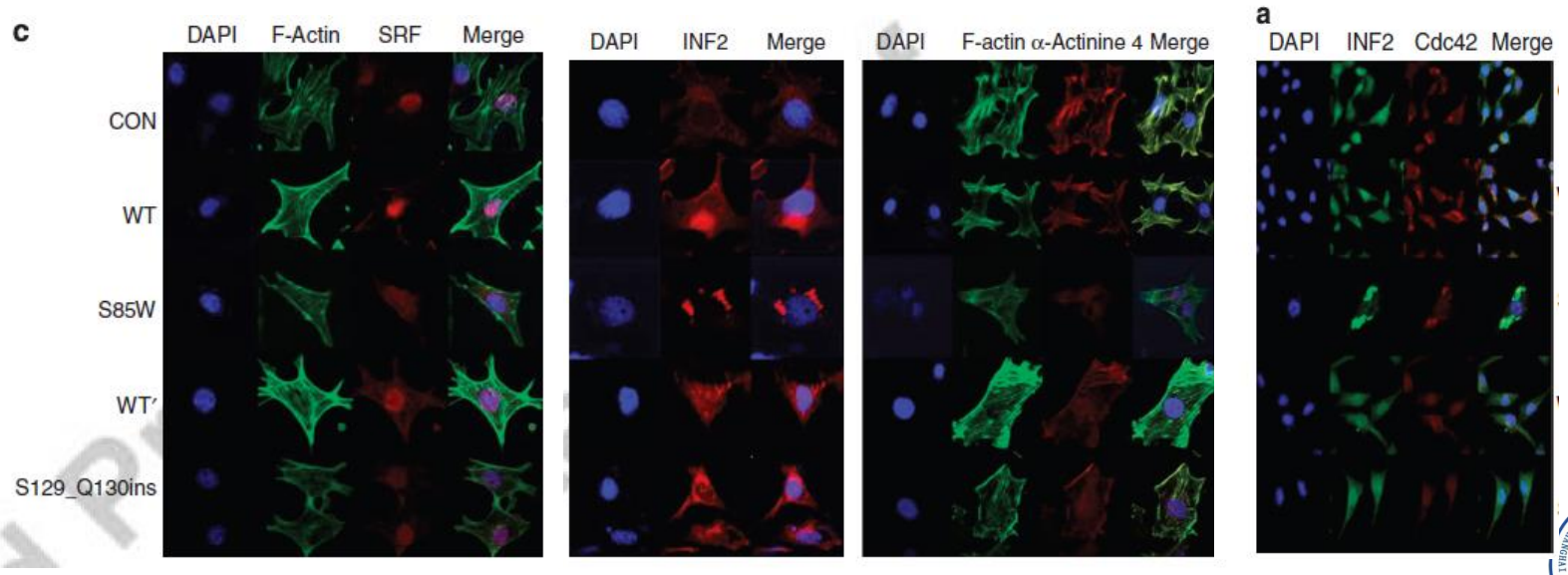
14q32 LOD: 3.52

***p.S85W* abolishes the hydrogen bonding network in the inner core of the protein**

Xie J, Hao X, …., Chen N. Kiidney international 2015

p.S85W affects the cytoskeleton

- **Mutation rate in our study is 3.6%.**
- ***p.S85W* mutation affects the interaction between *INF2* and *Cdc42*, which may lead to decreased activation of SRF, leading to abnormal cytoskeletal and morphological changes of podocyte**
- **The mechanism of *p.S129_Q130insVRQLS* mutation is still unknown**



Xie J, Hao X, …., Chen N. Kiidney international 2015

Family FSGS research 2 —gene sequencing

498 | *Journal of Molecular Cell Biology* (2014), 6(6), 498–505 doi:10.1093/jmcb/mju040

Article

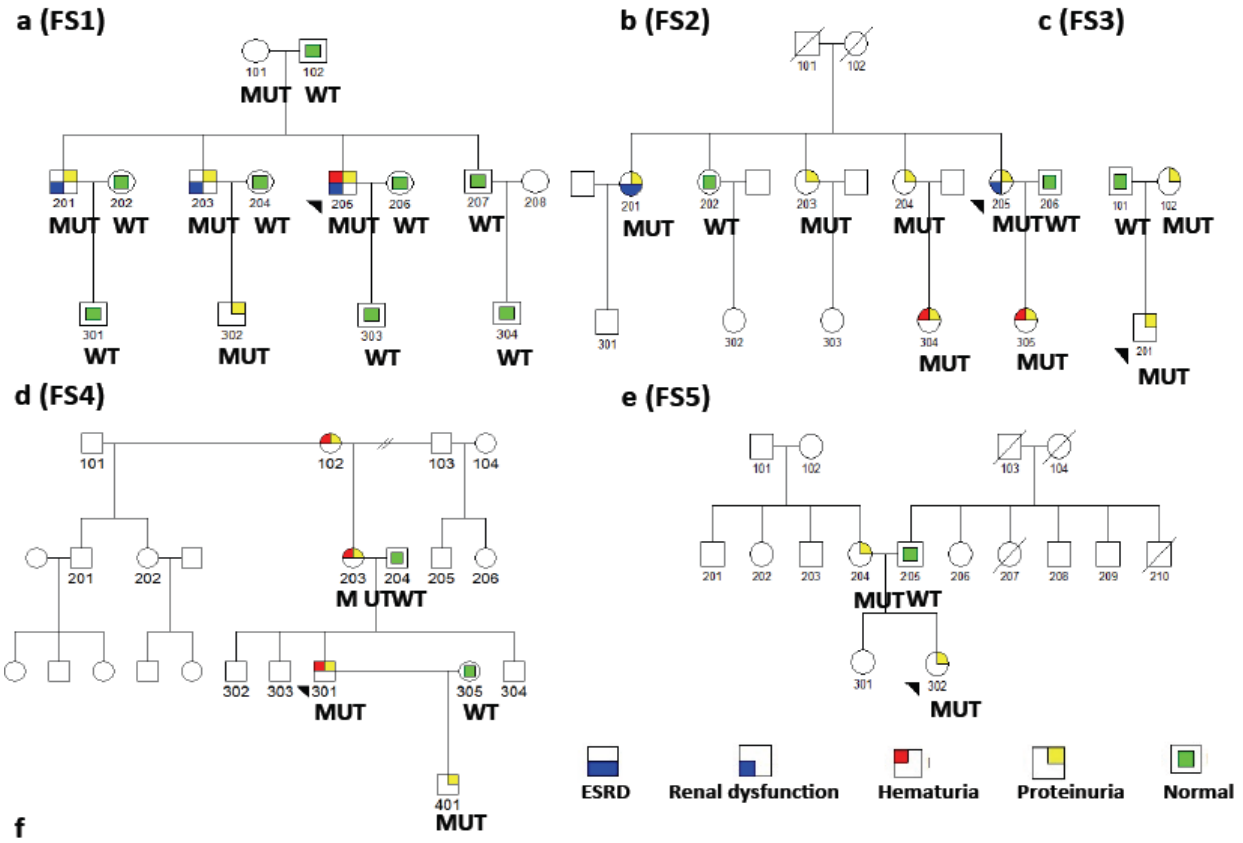
COL4A3 mutations cause focal segmental glomerulosclerosis

Jingyuan Xie[1,†], Xiaoxi Wu[2,†], Hong Ren[1], Weiming Wang[1], Zhaohui Wang[1], Xiaoxia Pan[1], Xu Hao[1], Jun Tong[1], Jun Ma[1], Zhibin Ye[3], Guoyu Meng[4], Yufei Zhu[2], Krzysztof Kiryluk[5], Xiangyin Kong[2], Landian Hu[2,*], and Nan Chen[1,*]

- 40 FFSGS families
  50 sporadic FSGS
- Methods: exome sequencing and sanger sequencing
- Exclude patients with *ACTN4*, *TRPC6* or *INF2* mutations

Xie J, Wu X, Ren H, Wang W, …, Chen N. Journal of Molecular Cell Biology 2014

COL4A3 mutations cause FFSGS

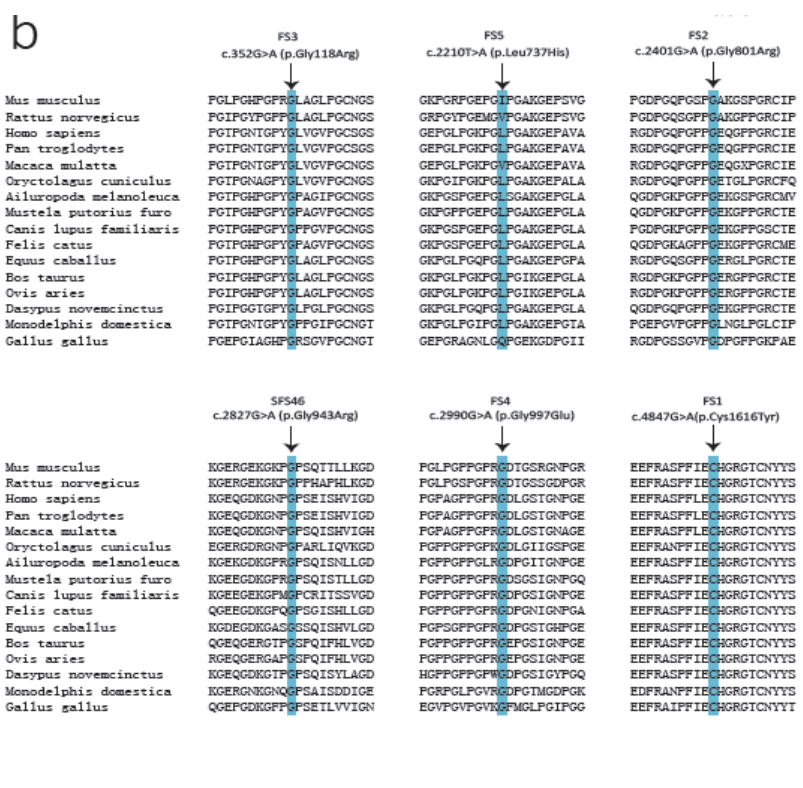


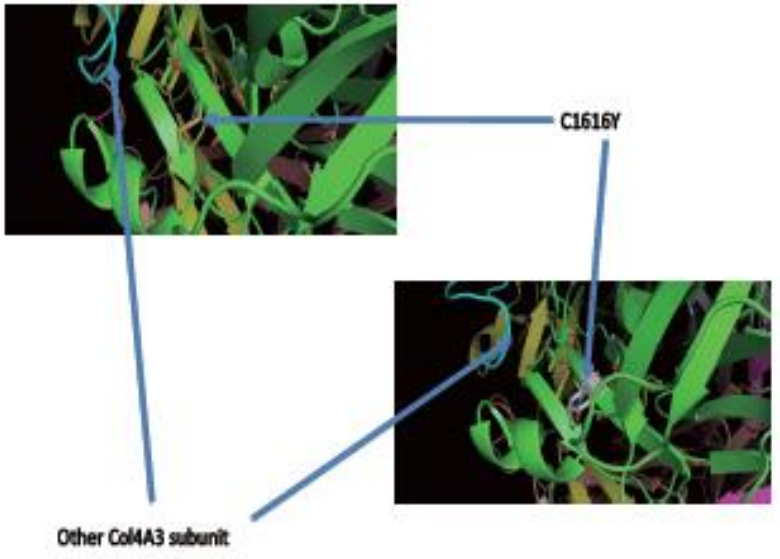
✓5/40 (12.5%)family with *COL4A3* heterozygous mutation

✓1/50 sporadic patients with *COL4A3* heterozygous mutation

Xie J, Wu X, Ren H, Wang W, …, Chen N. JMCB

Located in highly conserved regions





➢All six variants were located in a highly conserved region of *COL4A3*

➢Structural predictions: The *p.Cys1616Tyr* variant disrupts the

protein.

COL4A3 mutations cause FFSGS

Xie J, Wu X, Ren H, Wang W, …, Chen N. JMCB

COL4 mutations
the most frequent mutations in adult FSGS

Study design:

- 81 adults from 76 families;
- 24 families had a history of renal diseases
- Target NGS panel: covering 39 genes

Results:

- Confirmed pathogenic mutations: 10/81(12%)
- Probably pathogenic mutations：6
- Total mutation rate：16/81 （20%）
  - Familial 22%，sporadic 10%
  - *COL4A3-5 mutation：8/81（9.8%）*

Gene	CHR	Exons	Size (bp)
ACSL4	X	15	2364
ACTN4	19	21	2736
ALG1	16	13	1395
APOE	19	3	954
APOL1	22	7	1289
ARHGAP24	4	12	2478
ARHGDIA	17	6	683
CD2AP	6	18	1920
CFH	1	23	3710
COL4A3	2	52	5013
COL4A4	2	47	5073
COL4A5	X	53	5383
COQ2	4	7	1266
COQ6	14	13	1495
INF2	14	23	3817
ITGB4	17	40	5628
LAMA5	20	80	11088
LAMB2	3	32	5397
LMNA	1	18	2452
LMX1B	9	10	1453
MYH9	22	40	5883
MYO1E	15	28	3327
NEIL1	15	11	1865
NPHP4	1	31	4505
NPHS1	19	29	3726
NPHS2	1	8	1152
NXF5	X	14	1098
PDSS2	6	8	1200
PLCE1	10	33	7300
PMM2	16	8	741
PODXL	7	9	1677
PTPRO	12	27	3655
SCARB2	4	12	1437
SMARCAL1	2	16	2865
SYNPO	5	5	7560
TRPC6	11	13	2796
WT1	11	12	1648
ZEB1	10	11	3445
ZMPSTE24	1	10	1428

Christine Gast et al. Nephrol Dial Transplant(2015)0:1–10

Wessex Kidney Centre, Portsmouth Hospitals NHS Trust, Portsmouth, UK

Hereditary *COL4A3/COL4A4* variants mistaken for FFSGS?

DUKE study: *COL4A3* mutation rate in FFSGS is 10%

- ✓ Mutations in *COL4A3* and *COL4A4* are known to cause AS、TBMN
- ✓ Secondary FSGS is known to develop in classic AS at later stages
- ✓ In all 7 families, there were individuals with histologic features of FSGS by LM.
- ✓ In one family, EM showed thin GBM. other families had variable findings inconsistent with classical AS.

Kidney International (2014) 86, 1253–1259

Redefining the spectrum of the disease?

- A subset of renal manifestations associated with *COL4A3* or *COL4A4* variants cannot be distinguished from FSGS by clinical data or histopathology

- Redefining the spectrum of Alport syndrome?

Collegen IV related nephropathy

Kidney International (2014) 86, 1081–1083
doi:10.1038/ki.2014.326

Mutation rate of known genes in FSGS

	category	Number	Mutation rate	Reported rate
NPHS2	SRNS	44	0（0）	0-18%(children)
	FSGS	77	1（1.3%）	4-24%
ACTN4	FSGS	80	1（1.25%）	3.5%
TRPC6	FSGS	80	2（2.5%）	2.3~20%
INF2	FSGS	55	2（3.6%）	16%
COL4A3	FSGS	40	5（12.5%）	10%
Total			21.2%	35-80%

In over 70% pedigrees，no mutation is detected, indicating that lots of potential pathogenic genes need to be investigated.

Zhu B et al, Mutation Res 2009
Zhang Q et al, Contr Nephrol 2013
Clin J Am Soc Nephrol. 2011;6(5):1139-48

1 Overview

2 Pathogenesis

3 Diagnosis and Treatment

Study of FFSGS from Ruijin hospital

- **Patients：**
  - **2005~2012，124 FFSGS patients（83 families）**
  - **124 primary FSGS patients**

- **Diagnostic criterias of FFSGS：**
  - ✓ **More than one family member are biopsy-proven FSGS**
  - ✓ **One has biopsy-proven FSGS, other have proteinuria, progressive renal dysfunction or ESRD**
  - ✓ **AS, FD，TBMN or other hereditary kidney diseases were excluded**

Hong Ren,Nan Chen, Contrib Nephrol. 2013;181:101-8.

Study of FFSGS from Ruijin hospital

- **Basic information**
  - **Gender, age, blood pressure, first episode, disease course**
- **Laboratory examination**
  - **Blood/urine routine、24H urine protein, renal function**
  - **eGFR was calculated by MDRD**
- **Outcome**
  - **ESRD**
  - **Remission of proteinuria（at least 50% decline）**

Hao X,Nan Chen, Contrib Nephrol. 2013;181:101-8.

Baseline characteristics

Ruijin Hospital

Table 1. Clinicopathological characteristics of FFSGS and SFSGS

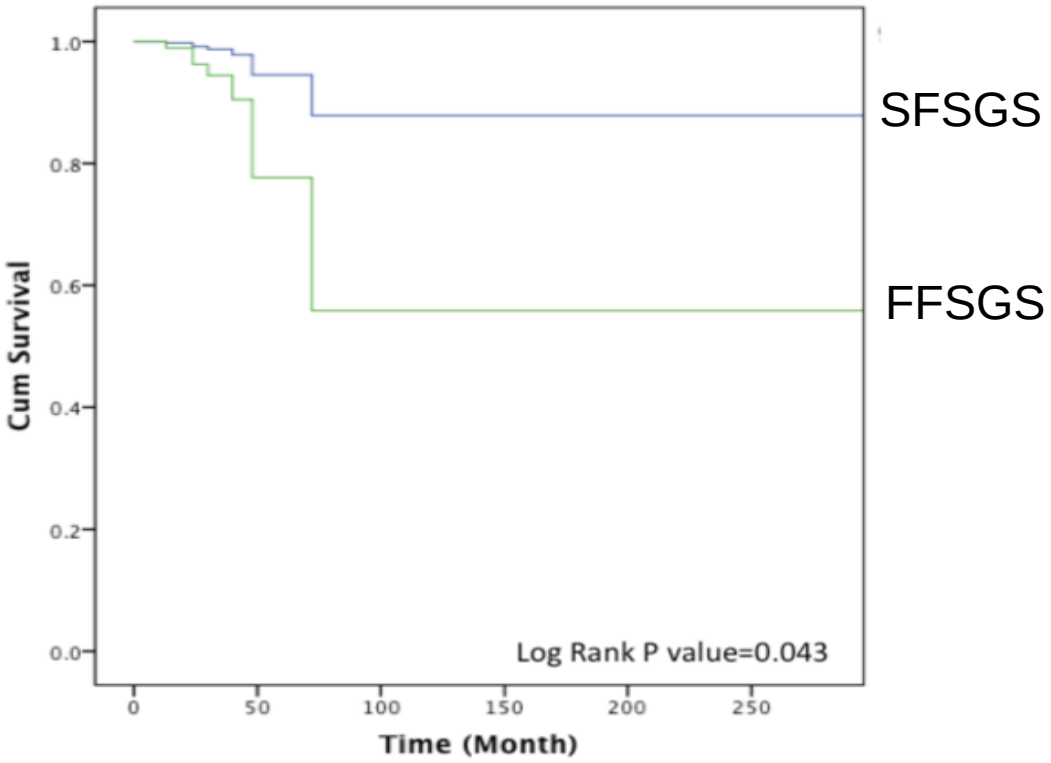
	FFSGS	SFSGS	p value
Number	124	124	
Male/female	71/53	76/48	0.096
Follow-up, months	28.3±12.5	26.5±19.5	0.081
Age of onset	34 (10–62)	40 (12–80)	0.035
Hypertension, %	43.75	35.16	0.079
Serum creatinine, μmol/l	174.3±186.6	153.0±144.2	0.086
Uric acid	415.6±118.1	397.9±109.4	0.275
eGFR, ml/min per 1.73 m^2	69.49±38.27	81.76±50.47	0.069
Hematuria, %	62.9	22.9	0.0001
Proteinuria, g/day	1.1 (0.03–5.6)	1.5 (0.05–8.7)	0.003
Nephrotic syndrome, %	13.3	22.6	0.029
Focal glomerulosclerosis, %	13.23±11.83	15.71±13.49	0.141
Global glomerulosclerosis, %	25.56±21.4	16.52±20.96	0.0007
Tubulointerstitial lesion score	4.07±0.28	3.00±0.1	0.0004
Remission of proteinuria, %	23.08	48.39	0.042
End-stage renal disease, %	27.42	2.42	0.003

Remission of proteinuria was defined as a proteinuria decline of at least 50% of the baseline level. Hematuria was defined as more than 3 red blood cells in each high-power field.

Hao X,Nan Chen, Contrib Nephrol. 2013;181:101-8.

Renal Outcome

	FFSGS	SFSGS	P
PR/CR	23.08%	48.39%	0.042
ESRD	27.42%	2.42%	0.003



Hao X,Nan Chen, Contrib Nephrol. 2013;181:101-8.

Comparison between FFSGS and SFSGS

Ruijin Hospital

FFSGS

- More hematuria
- Lower proteinuria
- Less NS
- More severe pathological lesions
- Less CR/PR
- More ESRD

SFSGS

- Higher proteinuria
- More NS
- Less severe pathological lesions
- More CR/PR

Hao X,Nan Chen, Contrib Nephrol. 2013;181:101-8.

KDIGO Guideline

Initial treatment

- **Steroid and immunosuppressive therapy be considered only in idiopathic FSGS associated with NS. (1C)**
- **Prednisone：a daily single dose of 1 mg/kg (maximum 80 mg) or alternate-day dose of 2 mg/kg (maximum 120 mg). (2C)**

KDIGO Guideline

Initial treatment

- **Initial high dose of steroids is given for a minimum of 4 weeks，up to a maximum of 16 weeks until complete remission (2D)**

- **Steroids be tapered slowly over a period of 6 months after achieving complete remission（2D）**

- **CNIs： first-line therapy ——patients with contraindications or intolerance to high-dose steroids (2D)**

KDIGO Guideline

Relapse treatment

- Same to MCD
- CTX 2-2.5mg/kg/d, po. 8wks（2C）
- For Recurrence patients after CTX treatment, CsA 3-5mg/kg/d or FK506 0.05-0.1mg/kg/d，po（2C）

Question 1——
Corticosteroid benefit for moderate proteinuria?

Design（RCT study）

- **Participants：primary FSGS patients with moderate proteinuria**
- **ACEI/ARB group(n=30), corticosteroid group(n=30)**
- **Follow-up:12 months**
- **Results：higher rate of proteinuria remission in corticosteroid group compared to ACEI/ARB group**

	group	0 m	6 m	p value	12 m	p value
proteinuria（g/24h）	ACEI/ARB	1.96±0.16 g	1.67±0.33	0.432	1.71±0.44	0.596
	corticosteroid	1.75±0.19 g	0.69±0.16	<0.001	0.48±0.12	<0.001

Hong Ren,Nan Chen, Contrib Nephrol. 2013;181:101-8

Question 2——
Extend duration of initial steroid treatment ?

Treatment: full dose of steroid ,N=65

Steroid treatment: 8 vs 12wks

Duration	CR	PR	NR	Effective rate
8 wks	30	15	18	70.31
12 wks	30	16	15	71.87

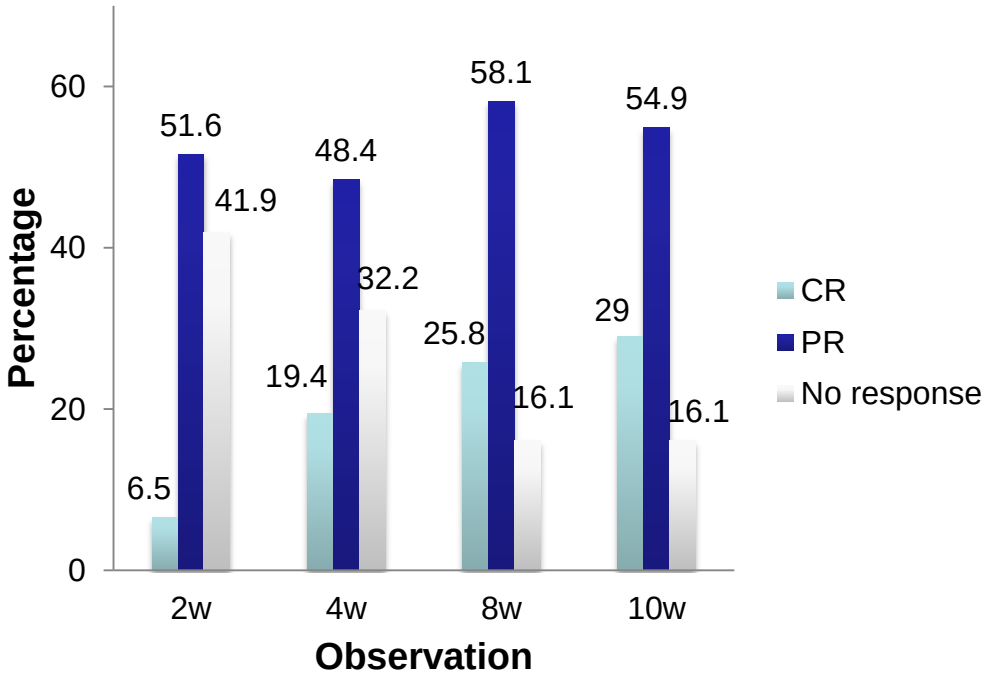
P>0.05

Extending steroid treatment to 12 wks resulted in a similar remission rate but more side-effects

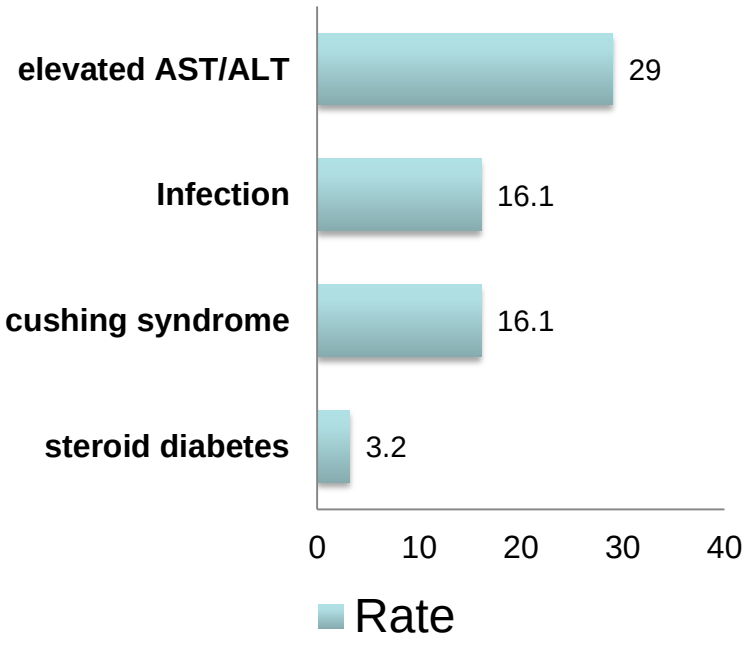
Nan Chen, WCN 2013：SU151

Question 2——
Extend duration of initial steroid treatment ?

Extending treatment to 10wks resulted in a same remission rate



Advent events in week 10



Zhang J, Liu ZH et al. CNDT, 2008 -18（1）， 13-19

Question 3:
Immunosuppressive Agents——CTX?

	CR	PR
steroid-sensitive+CTX	50%	25%
steroid-resistant+CTX	10%	10%

- CTX can be used as a second-line therapy?

Cochrane Database Syst Rev, 2008, 16, (3): CD003233.

Immunosuppressive Agents
FK-506

- **Participants：steroid-resistant FSGS（NS），N=44**
- **Follow-up：24 months**

Response to FK506

Parameter	Value	
Total remission	23 (52.2%)	
CR	17 (38.6%)	
Partial remission	6 (13.6%)	
Time to remit (weeks)	15.28 ± 6 (04–24)	
FSGS variants	TAC responsive	TAC resistant
FSGS-NOS ($n = 33$)	18 (54.5%)	15 (45.4%)
Cellular variant ($n = 08$)	3 (37.5%)	5 (62.5%)
Tip variant ($n = 03$)	2 (66.7%)	1 (33%)
Relapse during tapering	5 (21.7%)	
Relapse after completion of therapy	7 (30.4%)	
Complications	29 (65.9%)	

SR-FSGS, steroid-resistant focal segmental glomerular sclerosis; NOS, not otherwise specified; TAC, tacrolimus.

Nephrol Dial Transplant (2014) 0: 1–7

Immunosuppressive Agents
CTX vs FK-506

- **Participants： steroid-dependent or steroid-resistant FSGS**
- **CTX group N=18, FK506 group N=15**
- **Follow-up:12 months**
- **Result: CTX and TAC had a similar efficacy**

Table 3. Comparison of remission rate between CTX and FK-506 groups, n (%)

Duration	CTX			FK-506			p
	NR	remission		NR	remission		
		CR	PR		CR	PR	
6 months	8 (44.4)	10 (55.6)		5 (33.3)	10 (66.7)		0.77
		7 (38.9)	3 (16.7)		7 (46.7)	3 (20.0)	
12 months	6 (33.3)	12 (66.7)		4 (26.7)	11 (73.3)		0.97
		9 (50.0)	3 (16.7)		6 (40.0)	5 (33.3)	

CTX is preferable for its price

Hong Ren … Nan Chen. Am J Nephrol, 2013, 37: 84-90

immunosuppressive Agents
CTX vs FK-506

Adverse events	CTX (n = 18)	FK-506 (n = 15)	p
Infections*	9 (50.0%)	2 (13.3%)	<0.05
Sepsis	0	1	
Lung	2	1	
URTI	2	0	
UTI	4	0	
Herpes zoster	1		
Elevated glucose*	0	4 (26.7%)	<0.05
Elevated transaminase	1 (5.6%)	1 (6.7%)	NS
Deterioration of renal function	1 (5.6%)	0	NS
Menstruation disorders	1 (5.6%)	0	NS
Nausea/vomiting	2 (11.1%)	0	NS
Atopic dermatitis	1 (5.6%)	0	NS

NS = Non-significant difference; URTI = upper respiratory tract infection; UTI = urinary tract infection. * $p < 0.05$ indicates a significant difference between CTX and FK-506 groups.

Hong Ren … Nan Chen. Am J Nephrol, 2013, 37: 84-90

immunosuppressive Agents
CsA vs MMF

- **Multicenter, RCT**
- **Participants：** steroid-resistant FSGS, N=138

  (MMF group N= 66, CsA group N= 72)

- **Dose：** **CsA 4.6±1.7 mg/kg/d**

  MMF 26.2±6.1 mg/kg/d

- **Result：**
  - **Same PR and CR rate at 12 month（MMF 33% VS CsA 46%）**
  - **Same remission rate for extra 26 weeks.**

Gipson DS et al ,Kidney International , 2011,8: : 868-878

Question 4- Rituximab

- **Single center, prospective**
- **FSGS-NS patients, N=18**

（Steroid-dependent/resistant, CNI/MMF-resistant）

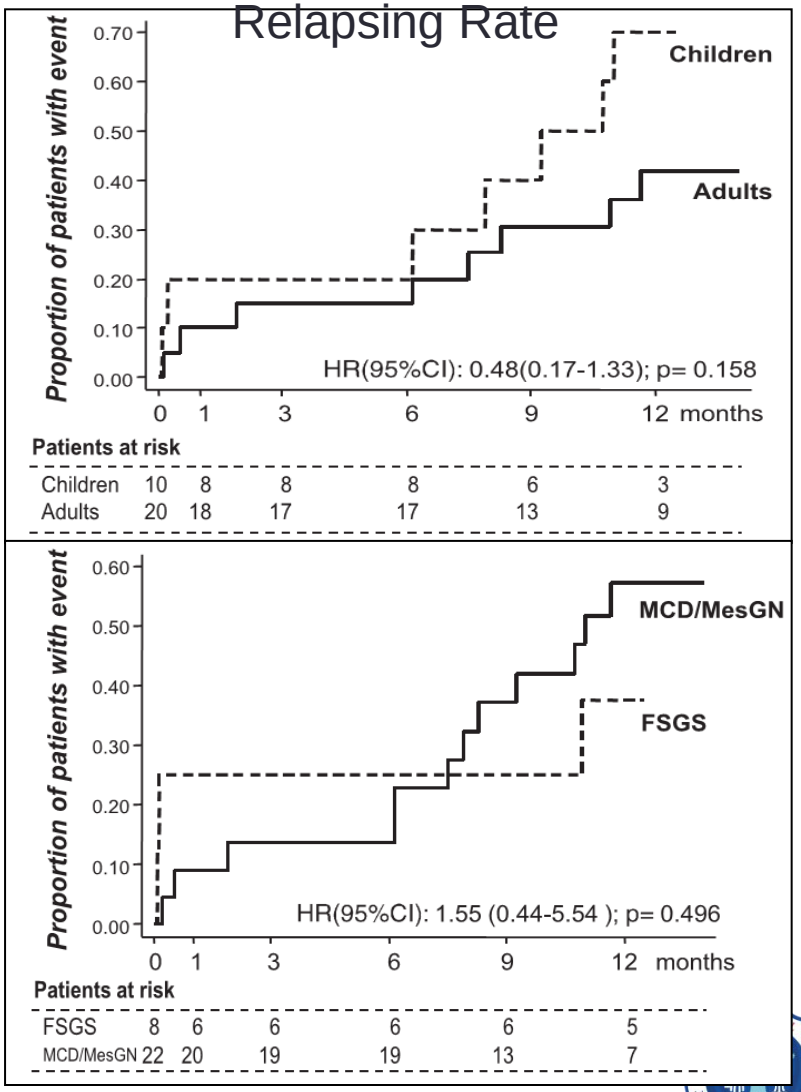
Treatment：Rituximab

	Before treatment		8m later		12m later	
FSGS	PR	NR	PR	NR	PR	CR
	10	8	17	1	17	1

El-Reshaid K.Saudi J Kidney Dis Transpl. 2012, 23(5):973-8.

Therapy—Rituximab

- Multi- center, prospective
- N=30
  - ✓ Children （N=10）
  - ✓ Adult （N=20）
  - ✓ MCD/MesGN (N=22）
  - ✓ FSGS (N=8)
- SDNS OR FRNS
- 1-2 doses of RTX（375mg/m^2）
- Follow-up: 1 yr
- Result：
  - ✓ 100% remission
  - ✓ 60% treatment-free
  - ✓ 50% never relapsed



J Am Soc Nephrol. 2014;25(4):850-63

Rituximab in treatment of refractory FSGS

- **Patients**： FSGS-NS, N=12 （SDNS, SRNS),

  no response to CTX, MMF, CsA/Tac, average duration 2-10 years）

- **Treatment**：
  - ✓ 375mg/m^2/w, 2-4 times
  - ✓ Tapering steroid and immunosuppressive agents within 3-6 months
  - ✓ Reapply Rituximab when CD19 count>1% or >15/ul
- **Follow-up**： 6-18 month
- **Efficacy** ： All achieved CR，no relapse

Ruijin Hospital unpublished data

Case Report

一般情况：男，17岁，学生

病史简介：

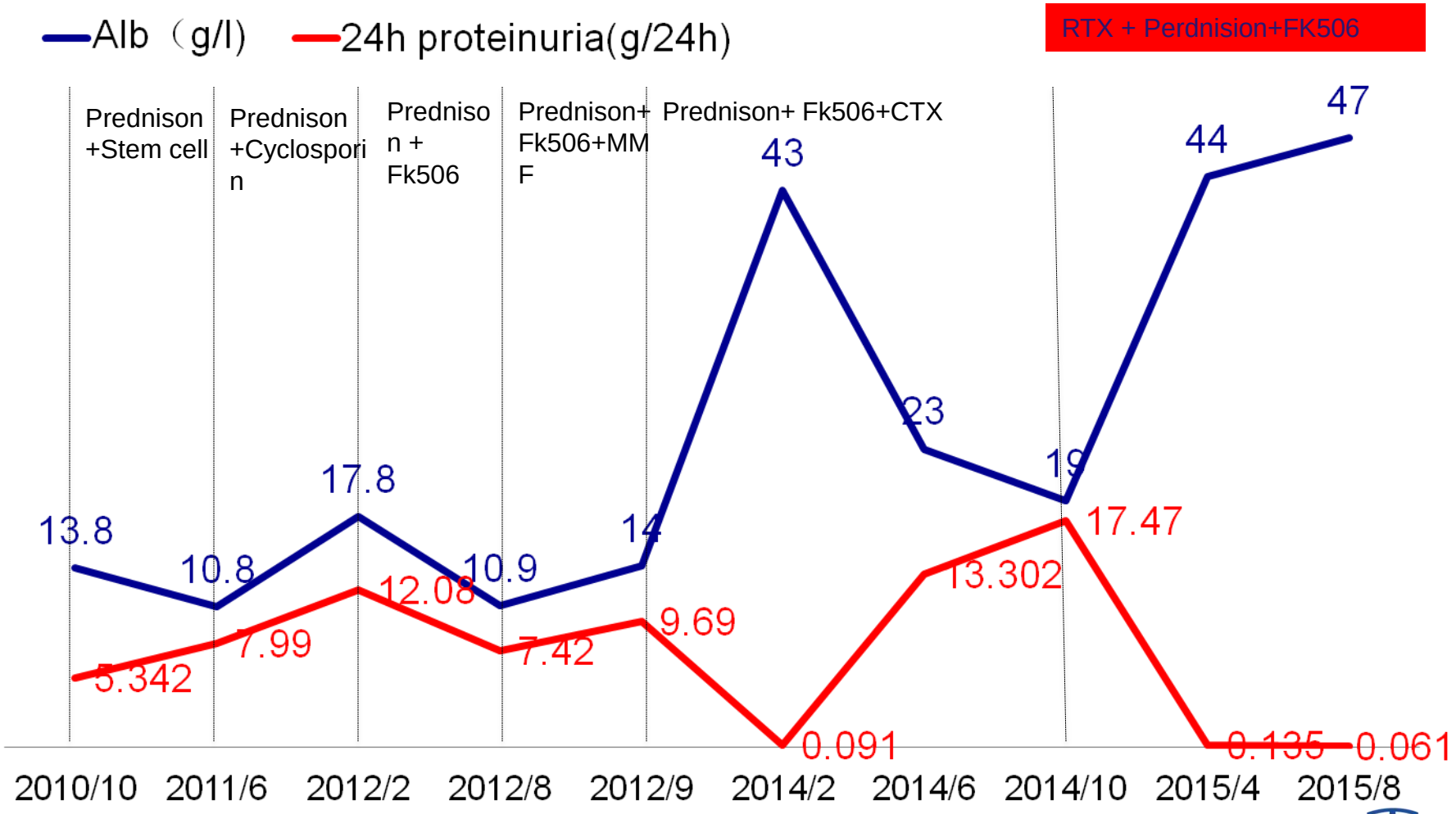
5年前无明显诱因下出现颜面、双下肢浮肿伴泡沫尿，2010年10月、2011年6月二次外院肾穿病理提示FSGS(NOS型），期间予“激素＋干细胞”（2010.10-11.6）、“激素＋环孢素”（2011.6-2012/2）、“激素＋FK506”（2012.2-2012.8）、“激素＋FK506+MMF”(2012.8-2012.9)治疗，治疗过程中NS一度缓解,但反复复发。2年前我院就诊，当时24蛋白定量16398-25889mg／24h，Alb19g/l，Scr41umol／l，调整治疗方案为“激素＋FK506＋CTX”(2012.9-2014.10)治疗，规范治疗15月后NS完全缓解,4月后因上感后NS再次复发。

查体：BP:115/62mmHg，神清、满月脸、双肺呼吸音偏低，心率80次／分，腹软，腹部皮肤紫纹明显，双下肢浮肿。

治 疗 经 过

- 2014.10考虑NS复发，在“激素40mg／d＋FK506 4mg／d”基础上加用美罗华 375mg/m2治疗。
- 2次疗程后（2014.10.27、2014.11.3),NS完全缓解，予激素减至25mg／d。
- 2014.12、2015.2再次分别予美罗华治疗，治疗期间病情稳定，激素、FK506逐渐减药。
- RTX治疗期间无药物相关性不良反应。
- 随访期间无复发及不良反应反应。

24h proteinuria and albumin before and after treatment



Ruijin Hospital unpublished data

B cell counts during the treatment

RTX Treatment	Durition (month)	Lymphpcyte (10^9/l)	CD19+ (%)	CD20+ (%)	CD19+ （个 / ul）
RTX (375mg/$m^{2)}$ + Perdnision (40mg)+ FK506(4mg/d)	1/4	4	4.2	4.4	168
	1	3.6	0.3	0.5	10.8
	2	3.5	0.1	0.5	3.5
	4	4.1	0.1	0.1	4.1
	6	4.1	0.1	0.1	4.1
	9	4.1	0.1	0.1	4.1

Ruijin Hospital unpublished data

Summary

- **Exact pathogenic genes only account for small part of FSGS**
- **Next-gen sequencing helps to explore novel genes**
- **Mutation rate of *INF2* in Chinese familial FSGS is 3.6%**
- ***COL4A3* mutations account for 12.5% of AD FSGS**
- **Reclassification of Alport syndrom is suggested, “Collagen IV related nephropathy” ?**

Summary

- **Heterogeneous clinical manifestations of FSGS**
  - **FFSGS less response to treatment and a worse renal prognosis**
- **Treatment:**

-lack of high-quality RCT study especially in Chinese patients

-steroid therapy could be considered for moderate proteinuria

-extend steroid treatment may not be suggested

-rituximab is promising but need more data

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