

THE ASNIT DAY: new hints

2008-2009

G.M. Ghiggeri

PAVIA, 2009

Main topics in nephrotic syndrome research 2008-2009

- **Genetics**
- **Mechanisms**
- **Therapy**
- **Stem Cells**

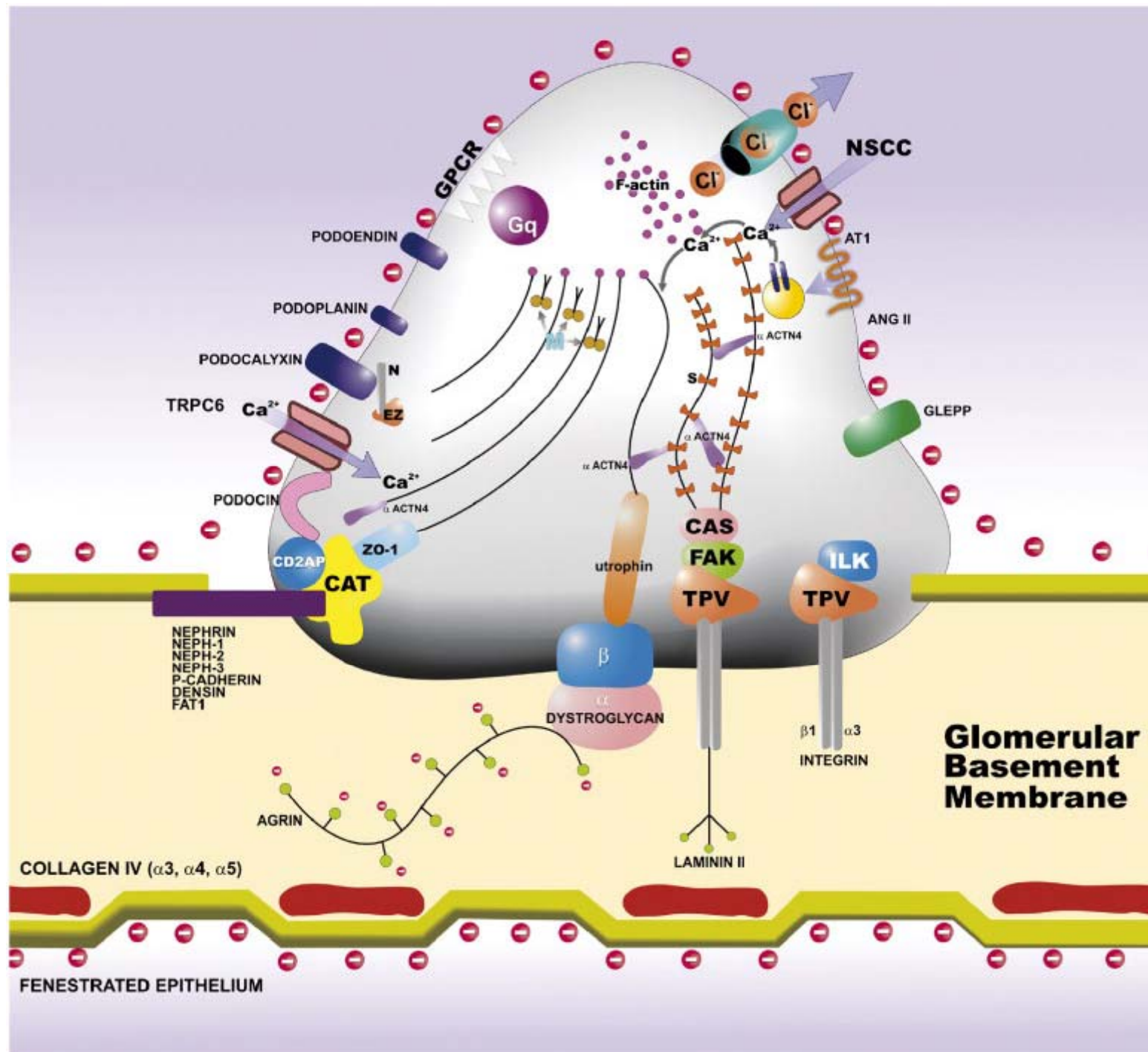


Table I: Principle genes involved in familial nephrotic syndrome and in associated syndromes.

	Gene	Locus	Protein	Inheritance	Prevalent Histology	#OMIM
Nephrotic Syndrome, Finnish type.	<i>NPHS1</i>	19q13.1	Nephrin	AR	DMS, microcysts	#602716
Nephrotic Syndrome, Steroid Resistant type 2	<i>NPHS2</i>	1q25-31	Podocin	AR	FSGS	#604766
Nephrotic Syndrome, Steroid Resistant type 3	<i>PLCE1</i>	10q23	Phospholipase C epsilon 1	AR	DMS	#610725
Denys-Drash Syndrome	<i>WT1</i>	11p13	Wilms tumor 1 gene	AD	DMS	#194080
Frasier Syndrome	<i>WT1</i>	11p13	Wilms tumor 1 gene	AD	FSGS	#136680
Focal Segmental Glomerulosclerosis type 1	<i>ACTN4</i>	19q13	Alpha-Actinin 4	AD	FSGS	#603278
Focal Segmental Glomerulosclerosis type 2	<i>TRPC6</i>	11q21-22	Transient Receptor Potential Cation Channel, homolog of 6	AD	FSGS	#603965
Focal Segmental Glomerulosclerosis type 3	<i>CD2AP</i>	6p12	CD2-associated protein	AR/AD	FSGS	#607832
<u>Syndromes</u>						
Schimke Immuno-Osseous Dysplasia	SMARCA L1	2q34-q36	SWI/SNF-Related, Matrix-Associated, Actin-Dependent Regulator of Chromatin, Subfamily a -Like Protein 1	AR	FSGS	#242900
Pierson syndrome	LAMB2	3p21	Laminin beta 2	AR	FSGS	#609049
COQ2 deficiency	COQ2	4q21-q22	Parahydroxybenzoate-Polyprenyltransferase	AR	FSGS, Collapsing	#607426
Leigh Syndrome	PDSS2	6q21	Decaprenyl Diphosphate Synthase, Subunit 2	AR	FSGS, Collapsing	#607426
AMRF syndrome (Action myoclonus-renal failure syndrome)	SCARB2/ LIMP2	4q13-q21	Scavenger Receptor Class B, Member 2	AR	FSGS	#254900

Network for molecular screening of n.s. in Italy

<i>NPHS1</i>	FG	Gesualdo
<i>NPHS2</i>	FG/GE	Ghiggeri
<i>WT1</i>	FG/GE	Gesualdo/Ghiggeri
<i>COQ2</i>	GE/RO	Emma/Ghiggeri
<i>PDDS</i>	GE/RO	Emma/Ghiggeri

PodoNet:



Consortium for Clinical, Genetic and
Experimental Research into Hereditary
Diseases of the Podocyte

Franz Schaefer, Heidelberg, Germany

Corinne Antignac, Paris, France

Aysin Bakkaloglu, Ankara, Turkey

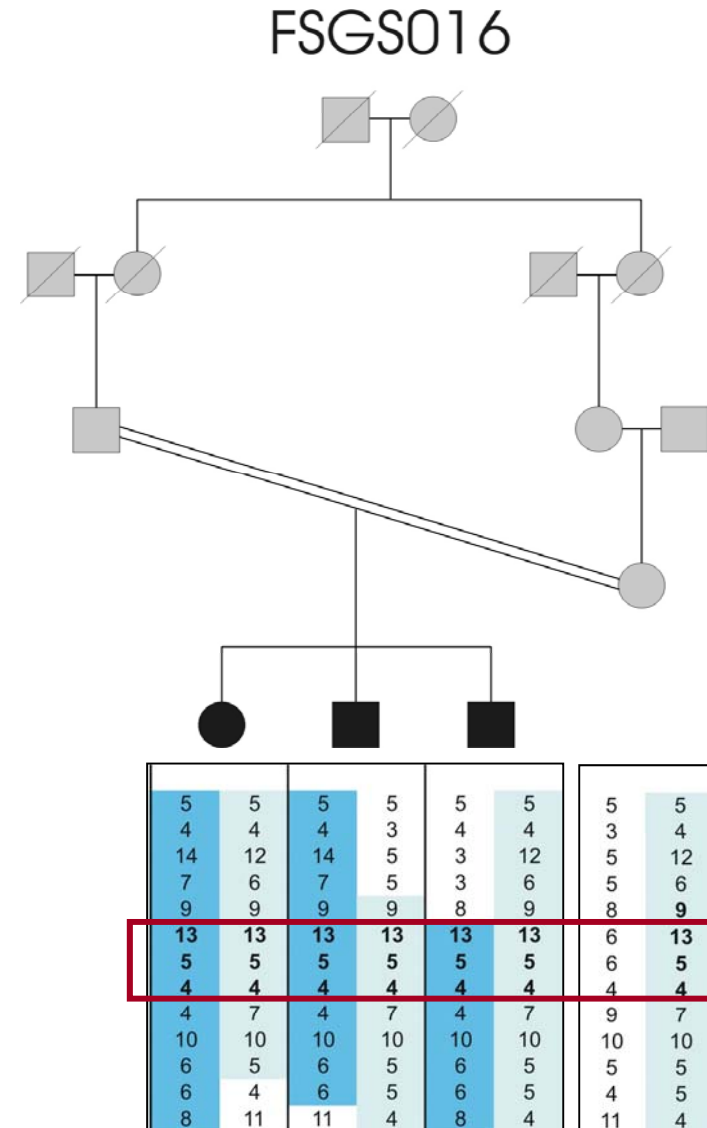
Francesco Emma, Rome, Italy

Gian Marco Ghiggeri, Genoa, Italy

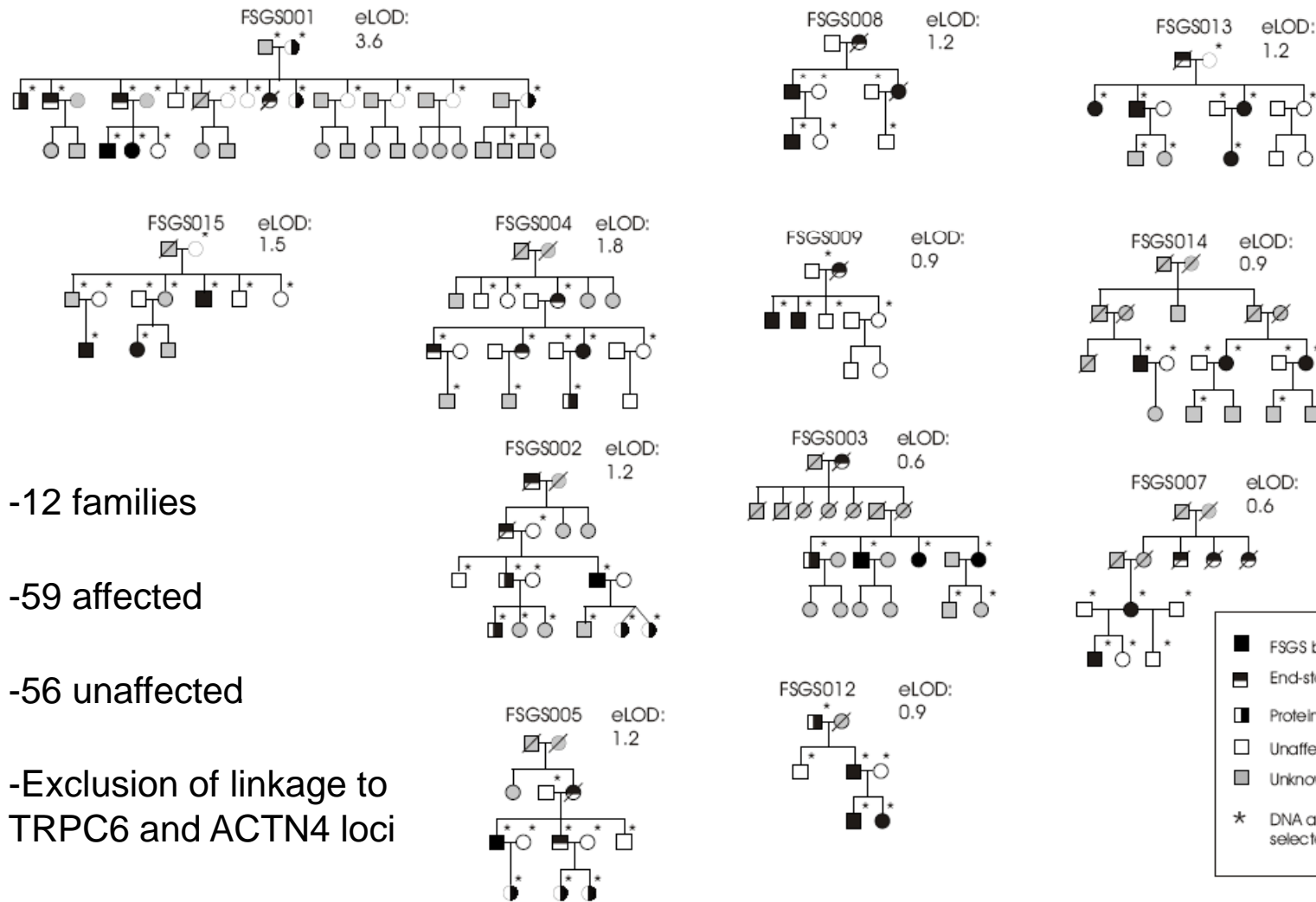
Guiseppe Remuzzi, Bergamo, Italy

GW SCAN AND HOMPOZYGOSITY MAPPING

- 393 microsatellites (~10cM spaced)
- Single peak across the genome (LOD~3)
- Evidence for homozygosity
- Localization of the 4th gene for SRNS (NPHS4)
- Fine mapping with 610 chips (Illumina)
- Refine in new families and sporadics



AUTOSOMAL DOMINANT FSGS



-12 families

-59 affected

-56 unaffected

-Exclusion of linkage to
TRPC6 and ACTN4 loci

FSGS: GENOME SCAN FOR LINKAGE

12 AD FSGS FAMILIES

GENOME WIDE SCAN

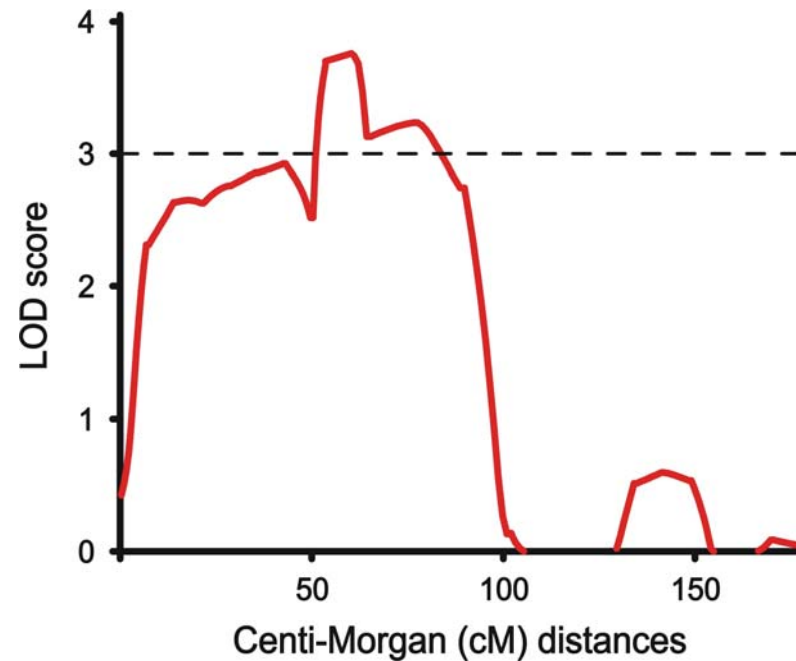


EVIDENCE FOR A NOVEL
LOCUS (FSGS4, HLOD=3.8)

INTERVAL TOO LARGE FOR
MUTATIONAL SCREENING



NEED FOR MORE FAMILIES



FSGS: RECURRENCE AFTER RENAL TX

FAMILIAL FORMS:

- Do not usually recur after renal transplantation
- Pathophysiologic insult primarily in podocytes
- Minor fraction of total FSGS cases

SPORADIC FORMS:

- High frequency of recurrence after renal tx
- Pathophysiologic mechanisms primarily extra-renal with secondary podocyte insult
- Major fraction of total FSGS cases

FAMILIAL FSGS: RECURRENCE

INDEX CASE:

FSGS at age 21

ESRD at age 25

TX at age 27

1 YEAR AFTER RENAL TX:

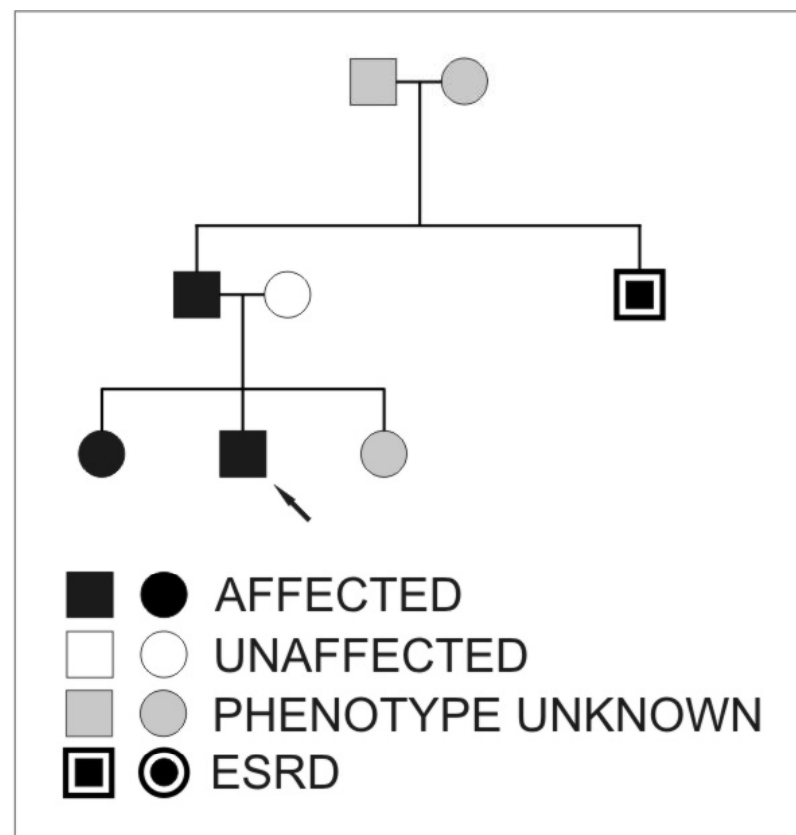
Nephrotic range proteinuria

Biopsy proven FSGS

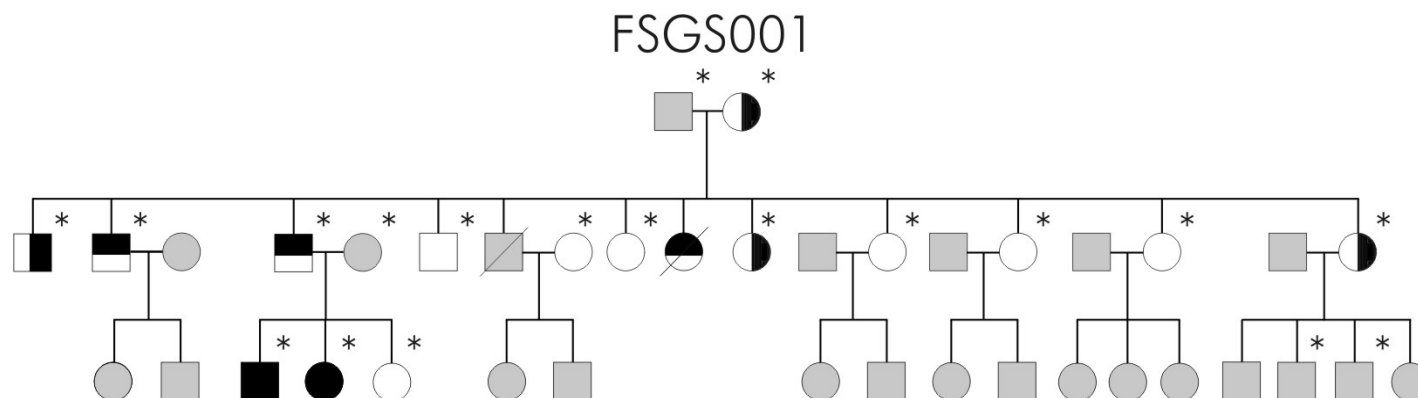
Negative plasma GPF

FAMILIAL EXTRA-RENAL

FORM OF FSGS



FSGS3001: LINKAGE SCAN



EXTENSION OF THE FAMILY

TOTAL EXPECTED LOD = 3.6

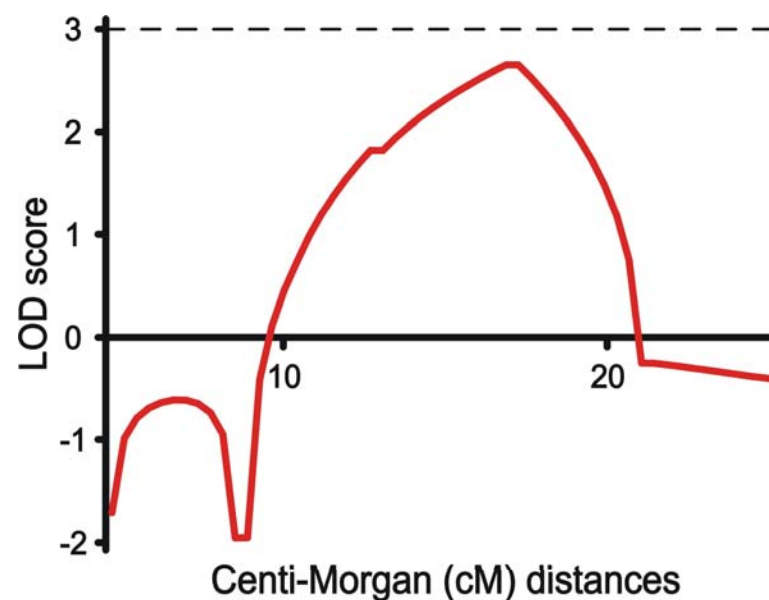


GENOME SCAN FOR LINKAGE



**SUGGESTIVE LOCUS (FSGS5,
LOD=2.8)**

**POTENTIAL NEW GENE RELEVANT
FOR COMMON FORMS OF FSGS**



ACKNOWLEDGMENTS



Ali Gharavi

Nephrology, Columbia University, NY



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Scolari**

Nephrology, Brescia, Italy



**Claudia
Izzi**



**Gian Marco
Ghiggeri**



**Gianluca
Caridi**

Pediatric Nephrology, IGG-Genoa, Italy



**Monica
Bodria**



Mechanisms for proteinuria

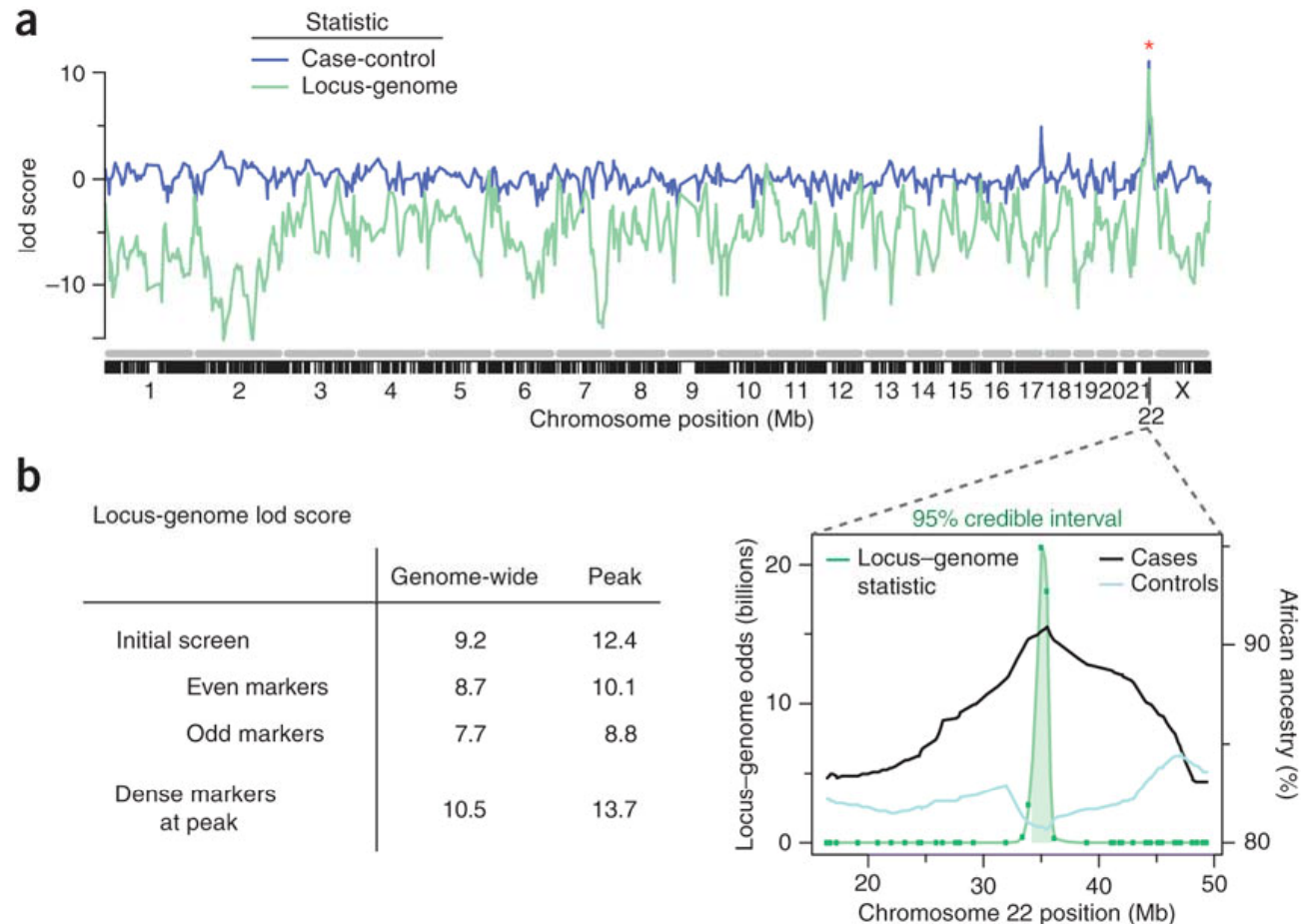
- **Podocyte cytoskeleton**
 - ACTN4
 - Myo IIa
 - Myo Ie
 - Synaptopodin

MYH9 is a major-effect risk gene for focal segmental glomerulosclerosis

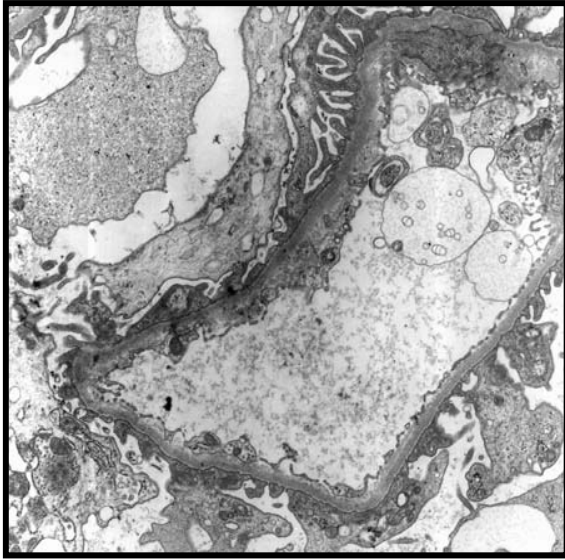
Jeffrey B Kopp^{1,17}, Michael W Smith^{2,16,17}, George W Nelson^{2,17}, Randall C Johnson², Barry I Freedman³, Donald W Bowden³, Taras Oleksyk², Louise M McKenzie², Hiroshi Kajiyama¹, Tejinder S Ahuja⁴, Jeffrey S Berns⁵, William Briggs⁶, Monique E Cho¹, Richard A Dart⁷, Paul L Kimmel⁸, Stephen M Korbet⁹, Donna M Michel¹⁰, Michele H Mokrzycki¹¹, Jeffrey R Schelling¹², Eric Simon¹³, Howard Trachtman¹⁴, David Vlahov¹⁵ & Cheryl A Winkler²

nature
genetics

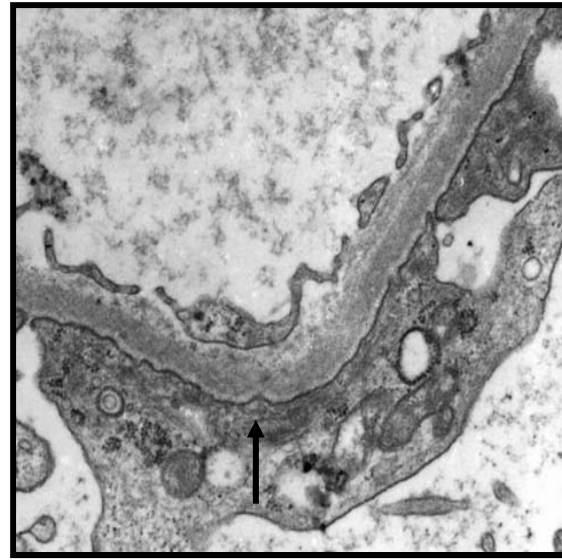
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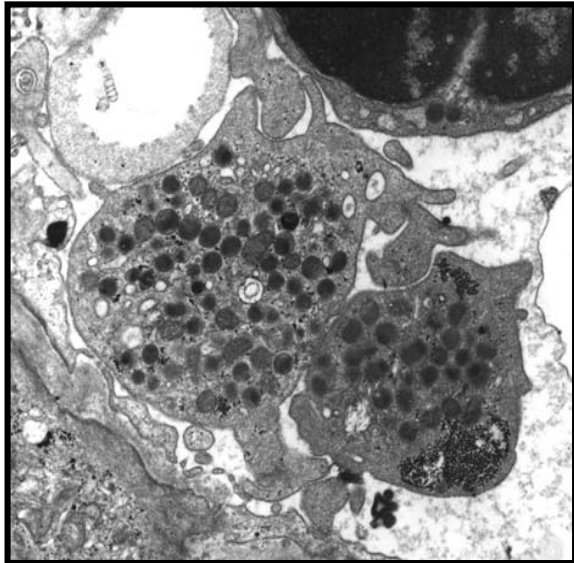
A



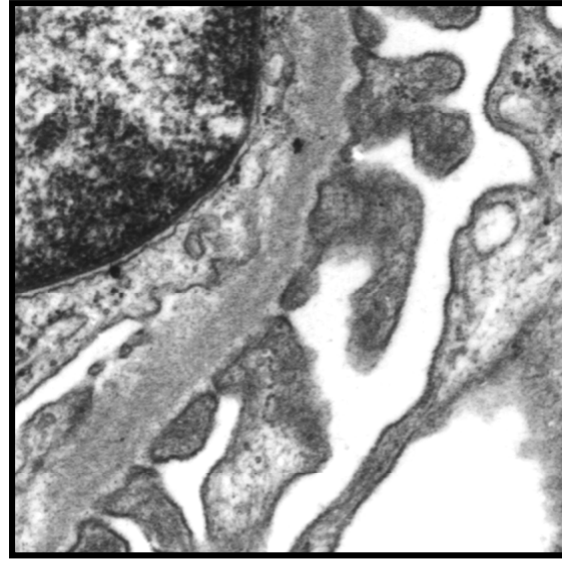
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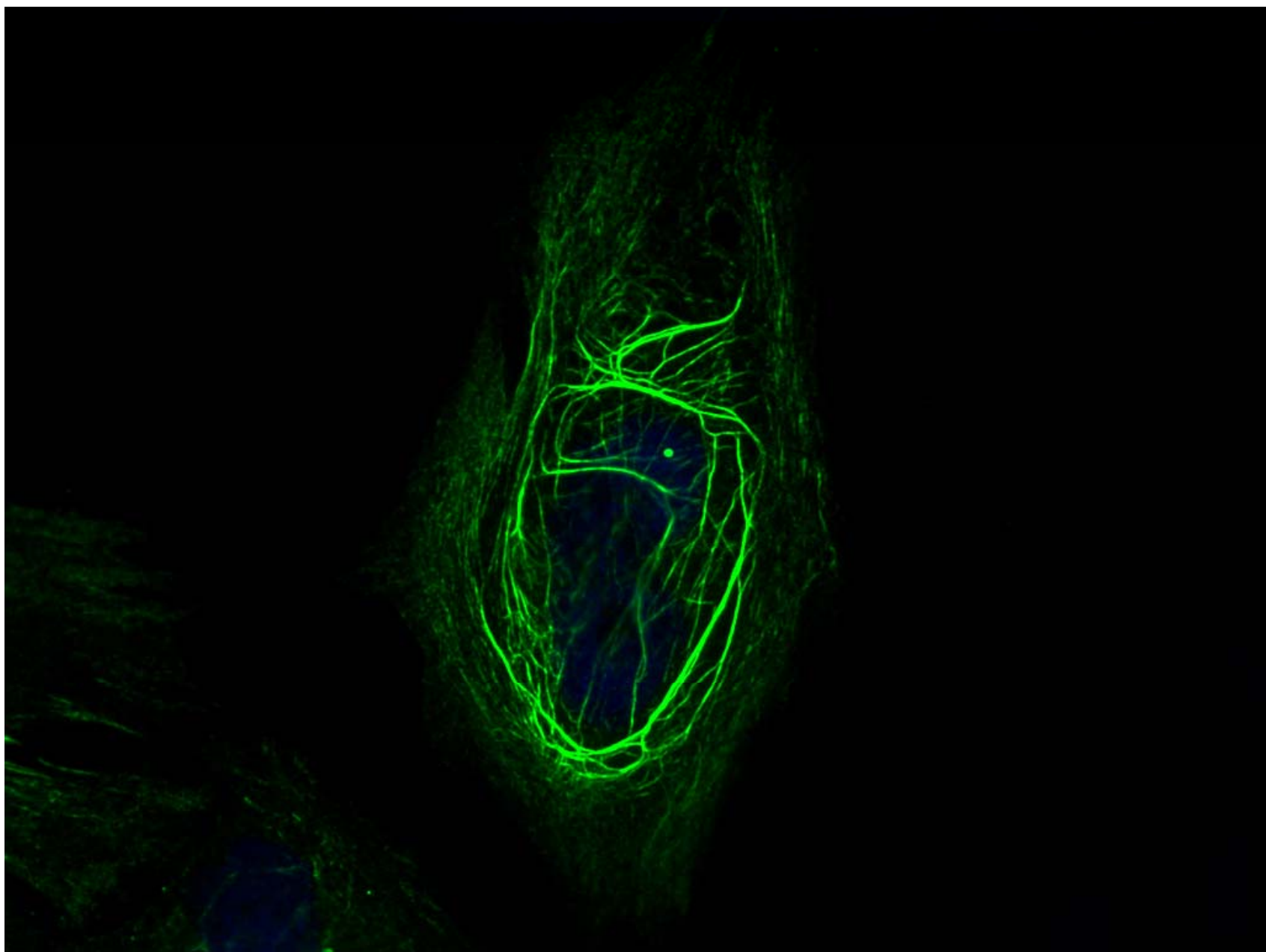


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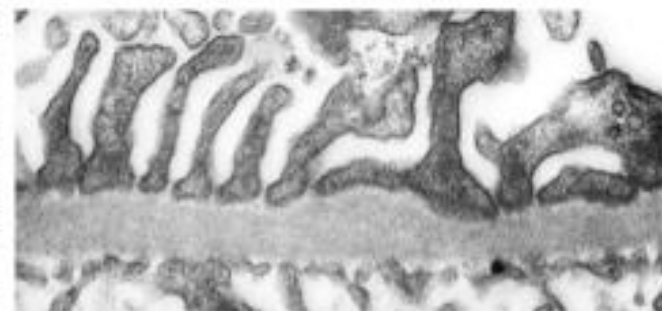
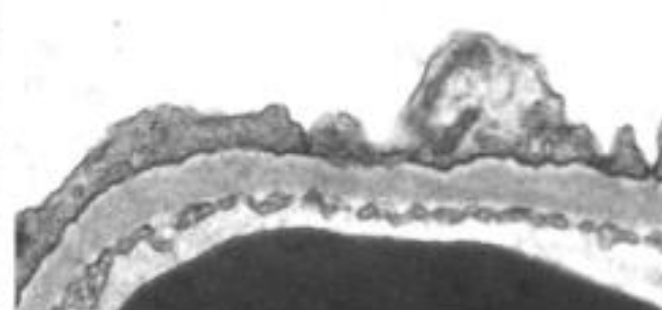
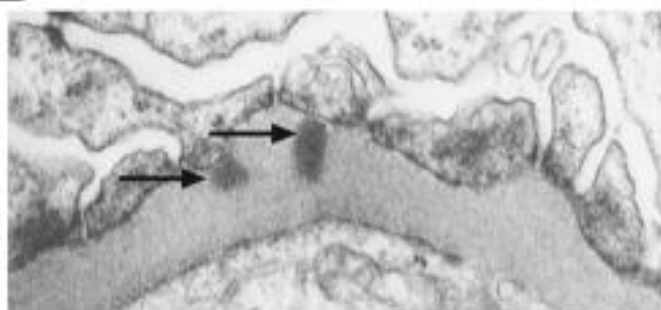
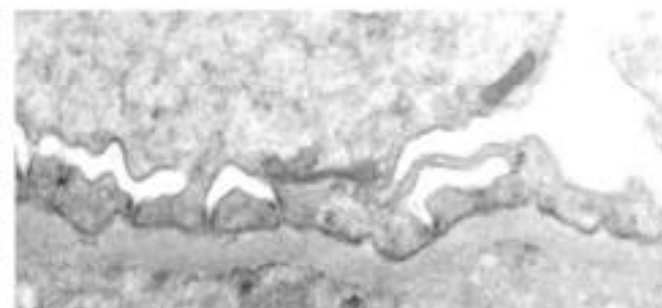
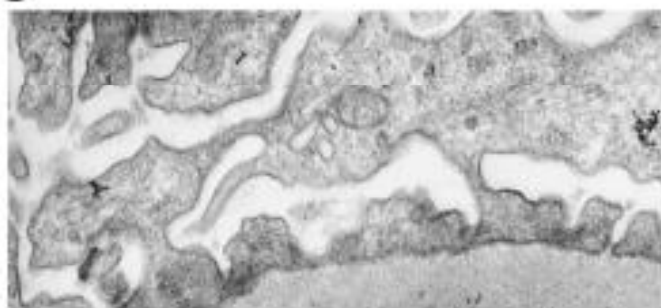
D





A

WT

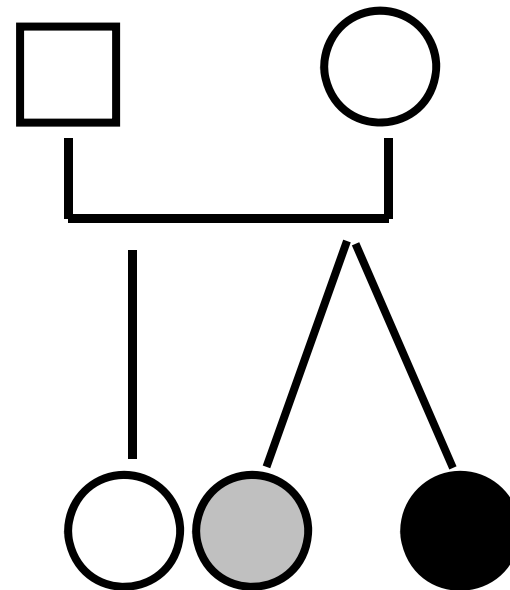
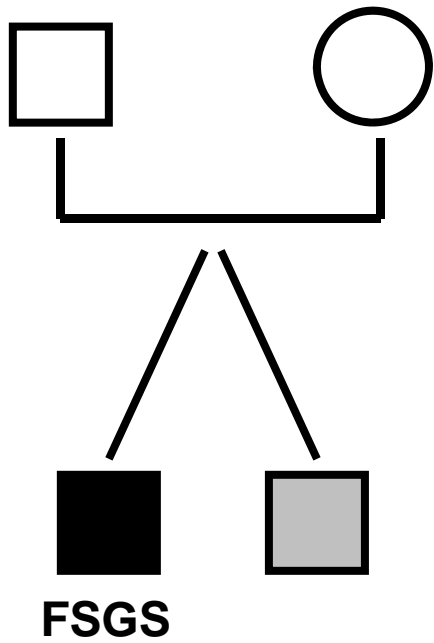
*Cd2ap*^{+/-}**B***Synpo*^{+/-}*Cd2ap*^{+/-}**C***Synpo*^{-/-}*Cd2ap*^{+/-}



Trigger



TWINS



Rats and mice

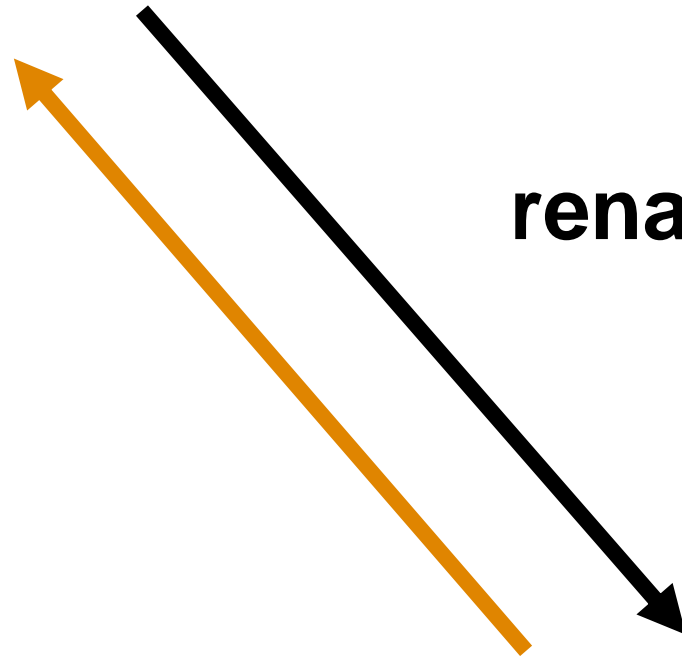
- ROP mice (vs C57) susceptibility to glomerular sclerosis after nephron reduction

Zheng et al KI 1998, Esposito et al AJP 1998

- *Susceptibility to ADR nephrosis in Sprague-Dawley, Zheng PNAS 2005, JASN 2007*

- **Buffalo / Mna rats,** *Le Berre et al JCI 2002*

Bufalo rats



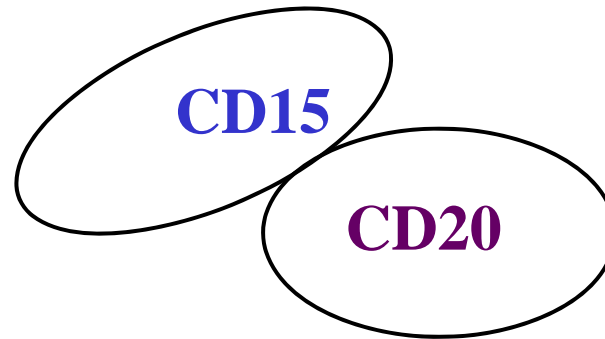
normal Lewis



Trigger:

- Fattore di permeabilità
- Treg
- Ossidazione

Treg



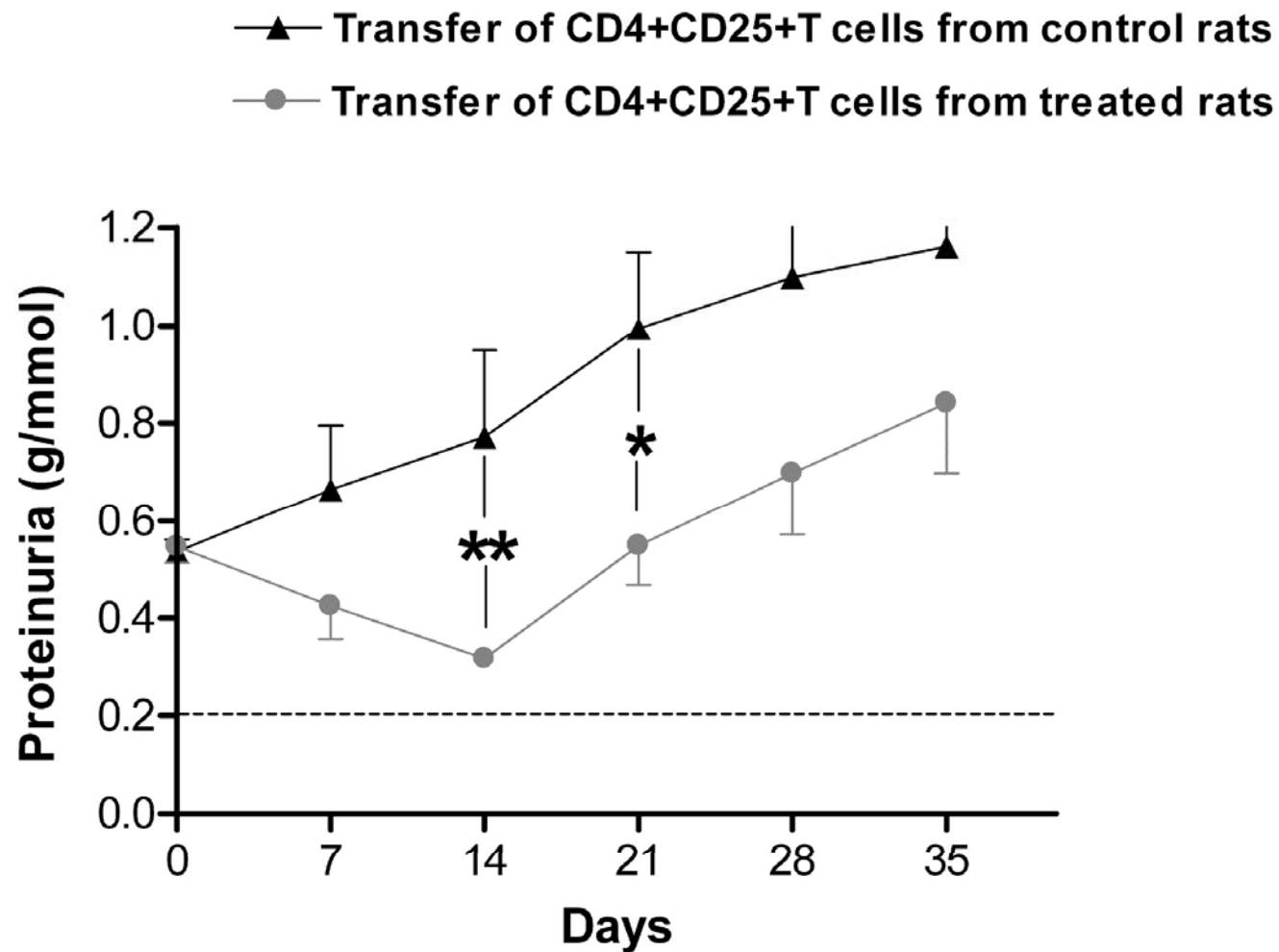
Induction of T Regulatory Cells Attenuates Idiopathic Nephrotic Syndrome

Ludmilla Le Berre,* Sarah Bruneau,* Jeanne Naulet,* Karine Renaudin,[†] Françoise Buzelin,[†] Claire Usal,* Helga Smit,* Thomas Condamine,* Jean-Paul Soulillou,* and Jacques Dantal*

*INSERM U643, and CHU Nantes, Institut de Transplantation et de Recherche en Transplantation, ITERT, and Université de Nantes, Faculté de Médecine, and [†]Service d'Anatomopathologie, CHU Hôtel Dieu, Nantes, France

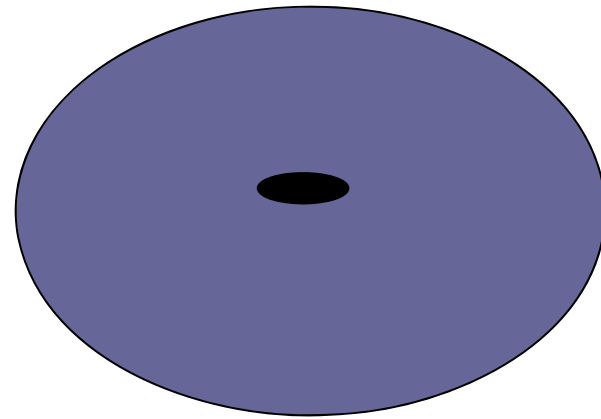
J Am Soc Nephrol 20: 57–67, 2009.

Figure 6. Transient regulation of nephropathy after transfer of CD4+CD25+ T cells from Buff/Mna rats in remission into Buff/Mna rats



Le Berre, L. et al. J Am Soc Nephrol 2009;20:57-67

NEUTROPHIL



TRY RESCUE

TheRapY of multidrug-RESistant nephrotic
syndrome in ChildrEn with RitUximab,

Ipotesi da testare

- effetto RTX nelle forme resistenti a PDN/CNI
- non inferiorità RTX a terapia standard nelle dipendenze PDN/CNI
- bilancio rischi/benefici

- Gruppo A: *resistenti a steroidi e CNI*

A1 12/12 Rituximab

A2 12/12 controllo terapia standard

- Gruppo B: *steroido-dipendenza con tossicità intolleranza PDN/CNI*

B1 12/12 Rituximab

B2 12/12 controllo terapia standard

2 boli RTX 375 mg/m² al T 0 e T 15 g

- Gruppo C: *steroido-dipendenza senza tossicità
intolleranza PDN/CNI*

C1 15/15 Rituximab

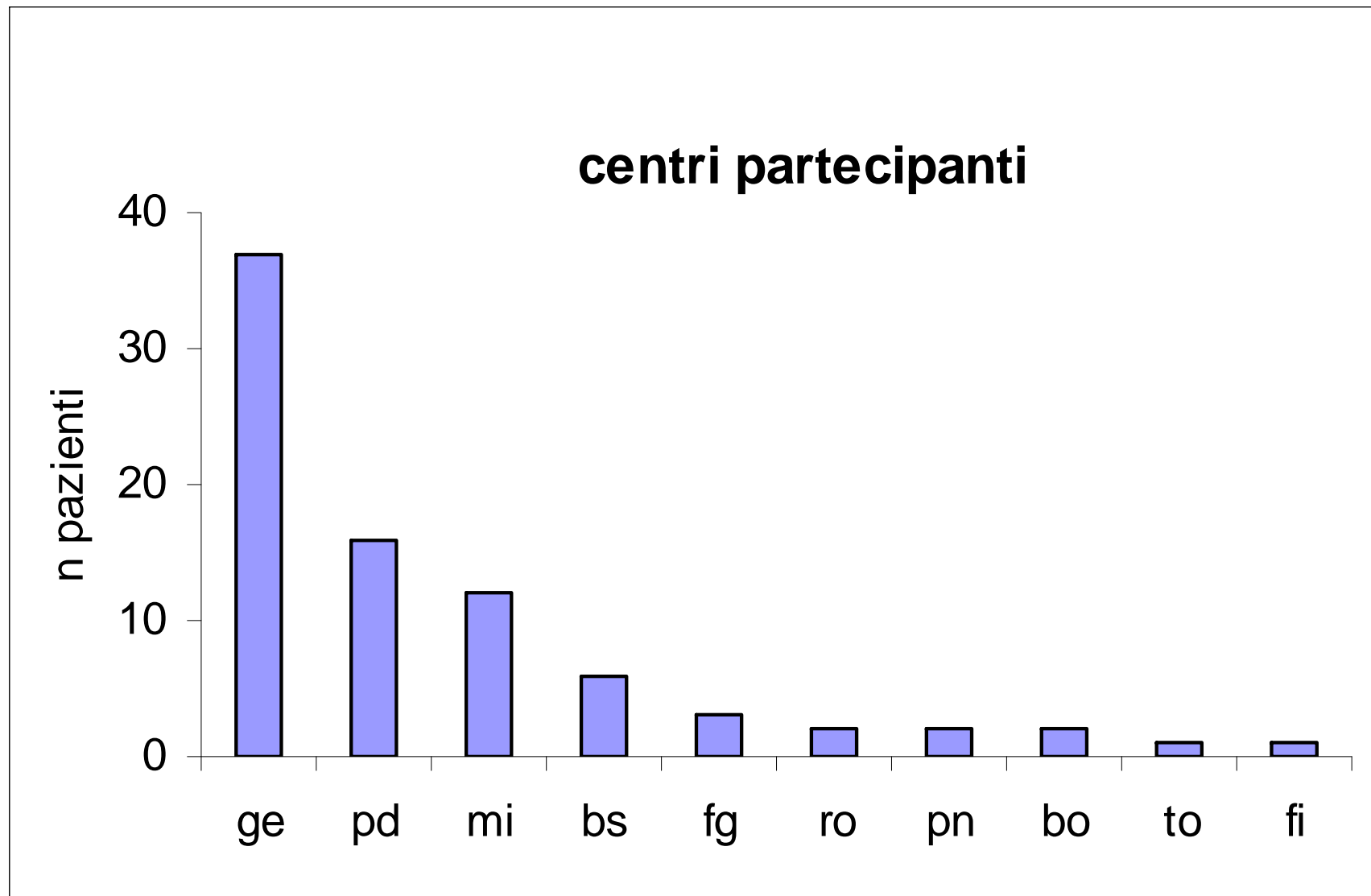
C2 15/15 controllo terapia standard

- Gruppo D: *steroido-dipendenza monoterapia*

D1 5/15 Rituximab

D2 3/15 controllo terapia standard

1 bolo RTX 375 mg/m² al T 0



Stem Cells

- **Mesenchimal Stem Cells**
- **Podocyte stem cells**

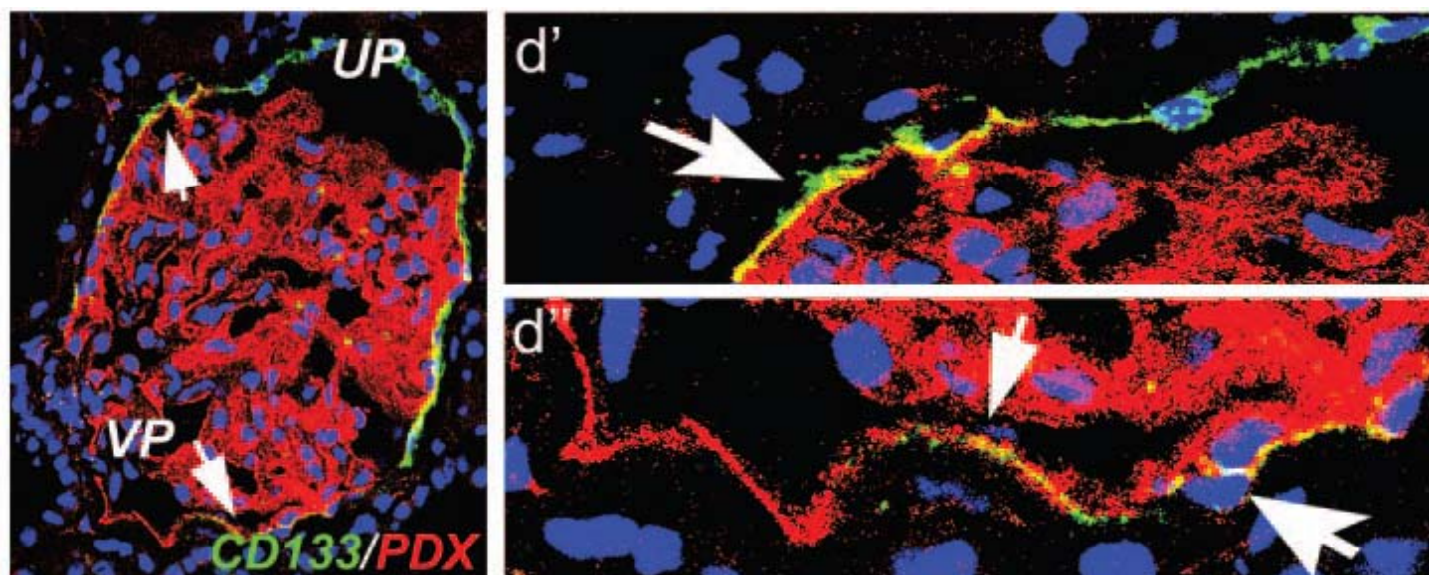
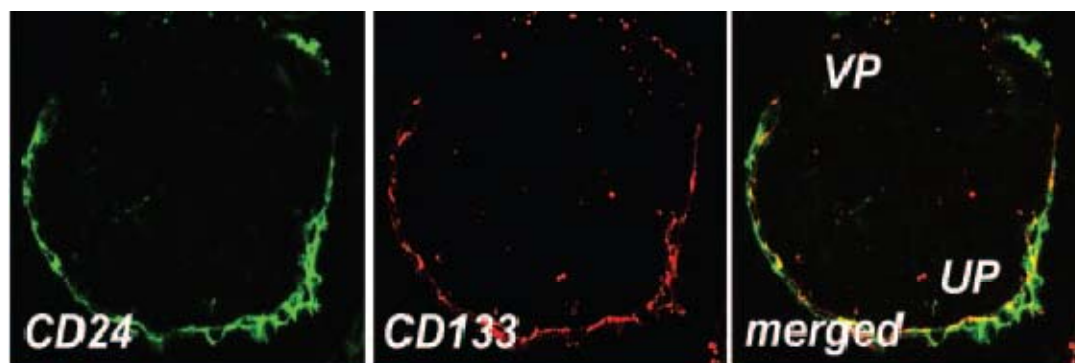
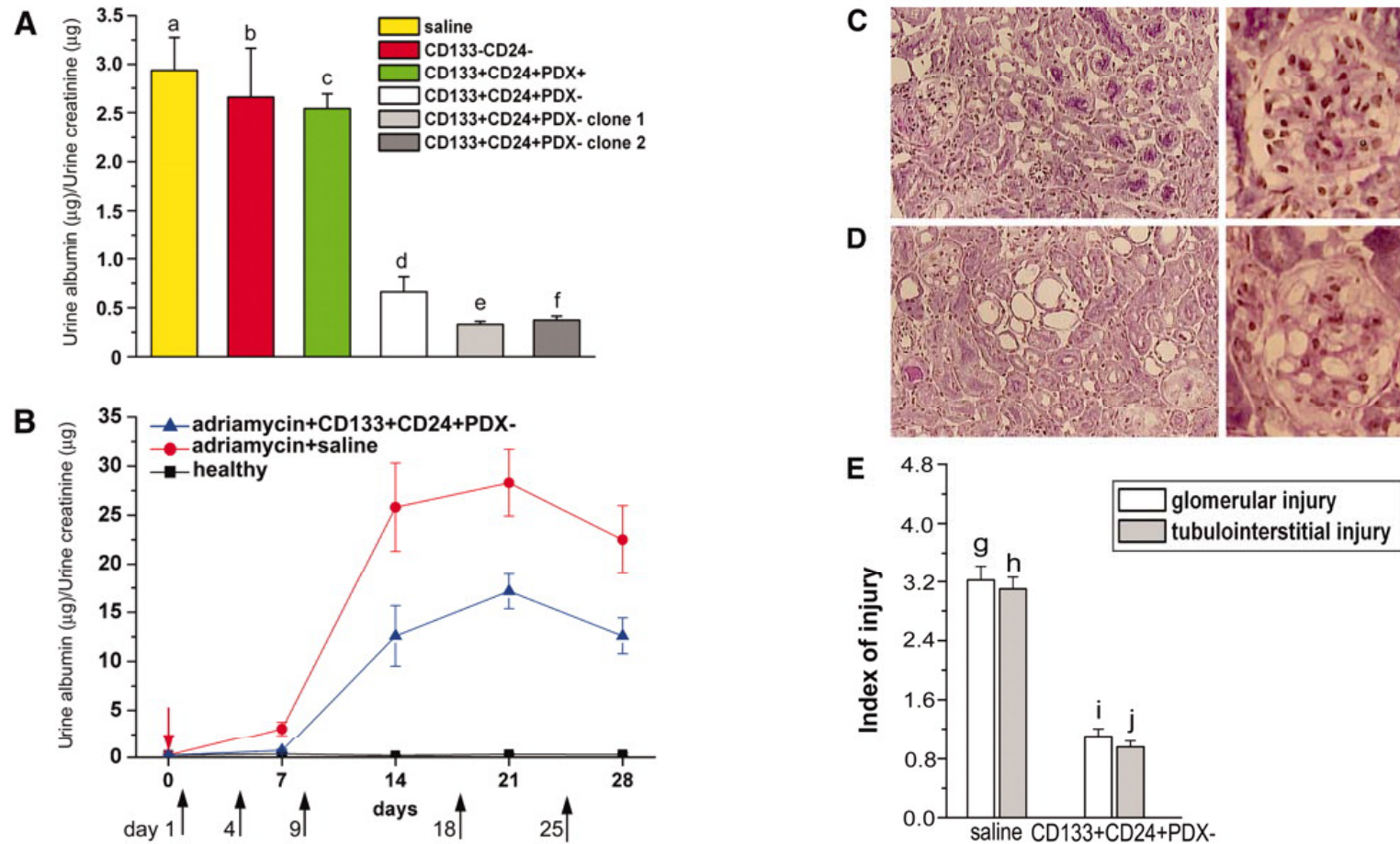


Figure 4. CD133+CD24+PDX- cells, but not CD133+CD24+PDX+ or CD133-CD24- cells, reduce proteinuria and improve glomerular and tubulointerstitial injury in SCID mice affected by adriamycin-induced nephropathy



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- G. Caridi
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- F. Emma
- A. Gharavi
- S. Sanna-Cherchi
- R. Gusmano
- The Kidney Foundation
- Wilma Querci Foundation

Call for a position in clinical research at IGG.

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