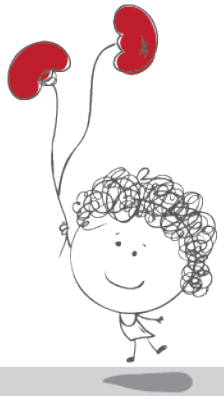
Doença renal em Pediatria: Uma abordagem translacional

Ana Cristina Simões e Silva, MD, PhD
Professor Titular, Departamento de Pediatria
Unidade de Nefrologia Pediátrica
Laboratório Interdisciplinar de Investigação Médica
Faculdade de Medicina, UFMG



Sumário

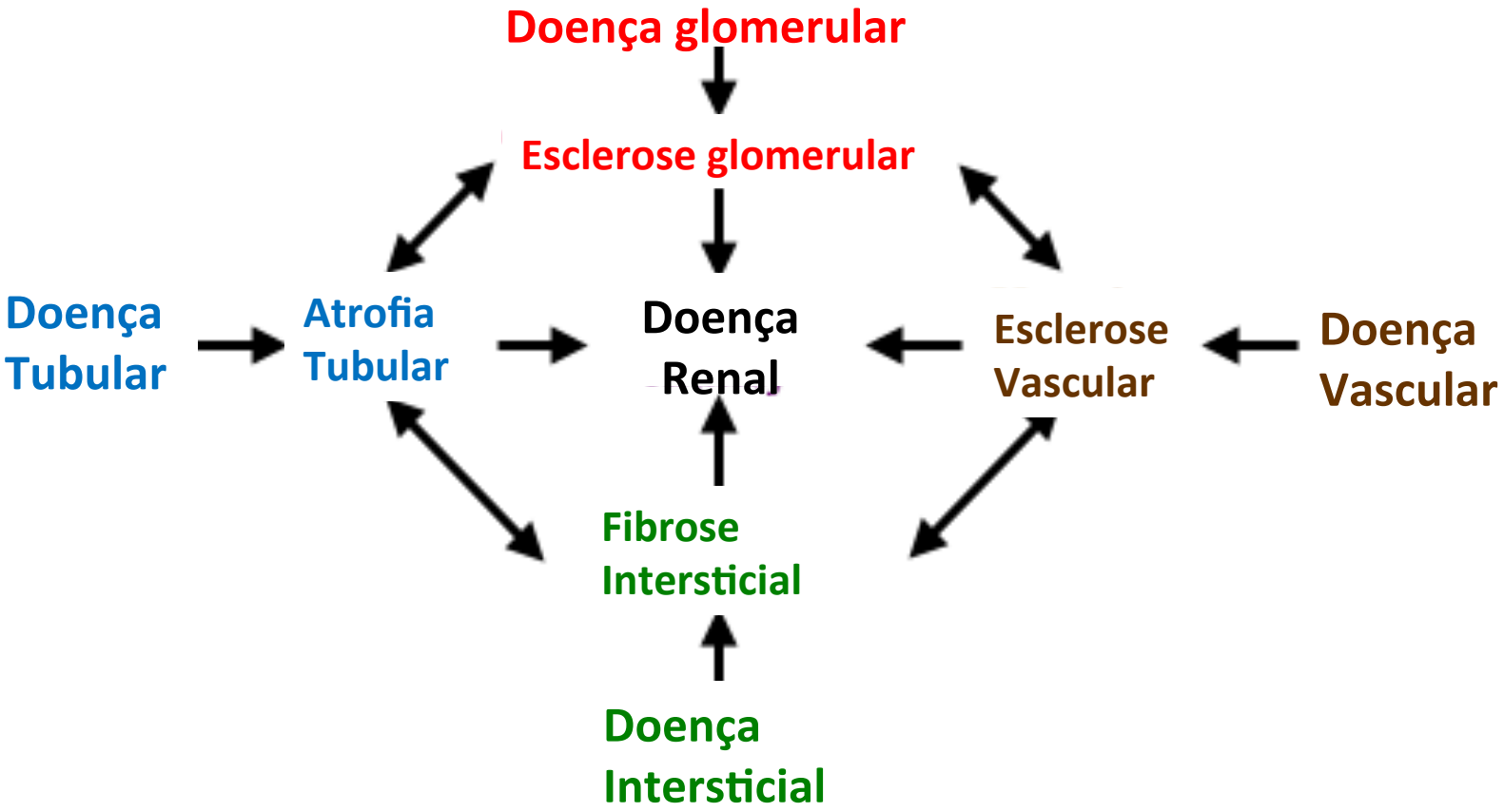
Doença renal

Dados latino-americanos e brasileiros sobre doença renal crônica são escassos (doença silenciosa e subnotificação).

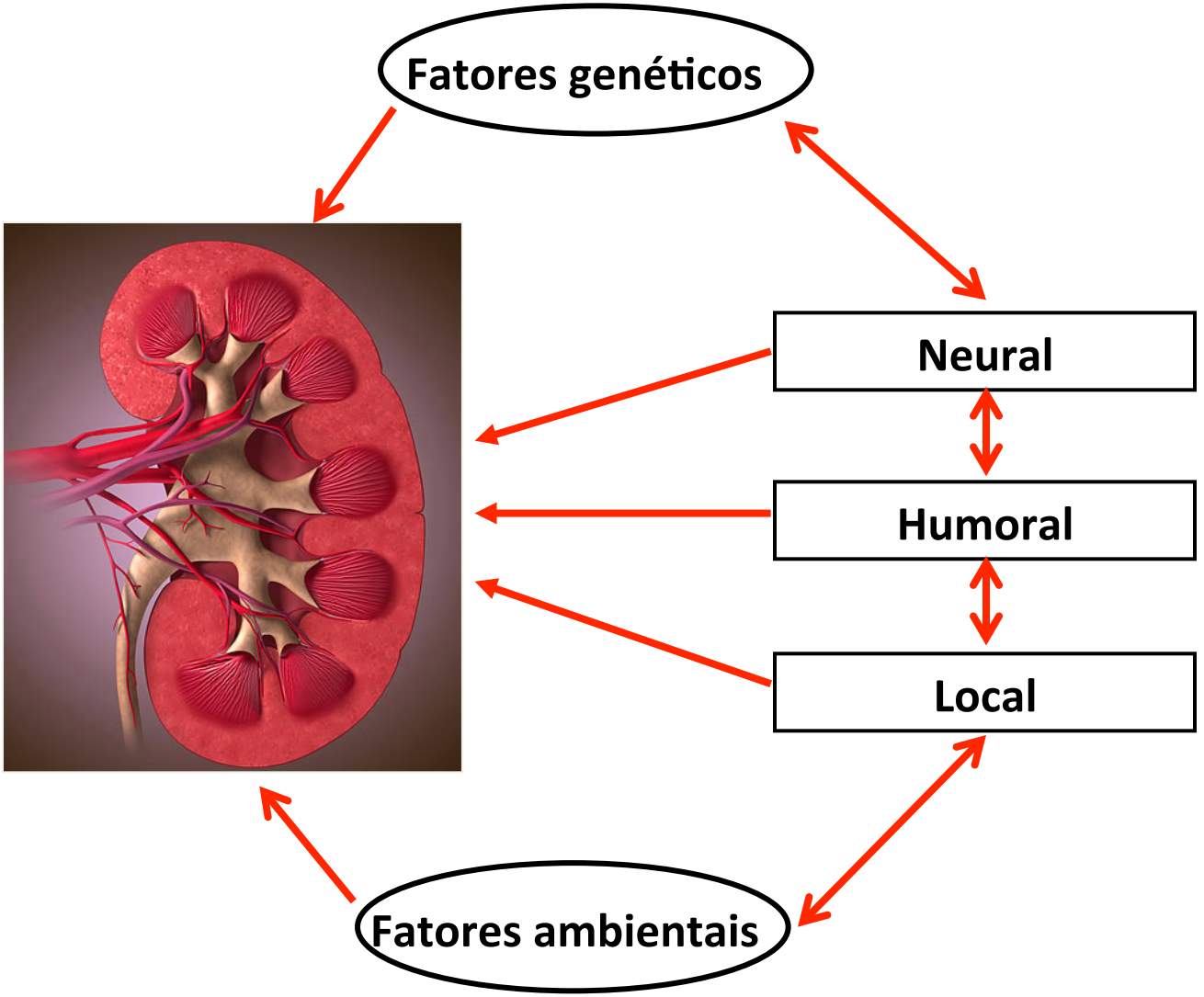
O Third National Health and Nutrition Examination Survey dos Estados Unidos em 2005 estimou que 11% da população americana adulta seja portadora de algum grau de doença renal crônica e mais de 8 milhões tenham ritmo de filtração glomerular < 60ml/min/1,73 m2.

A doença renal crônica terminal tem aumentado no Brasil e apresentado mortalidade superior, em números absolutos, a da maioria das neoplasias.

Doença renal



Doença renal



Síndrome Nefrótica Primária

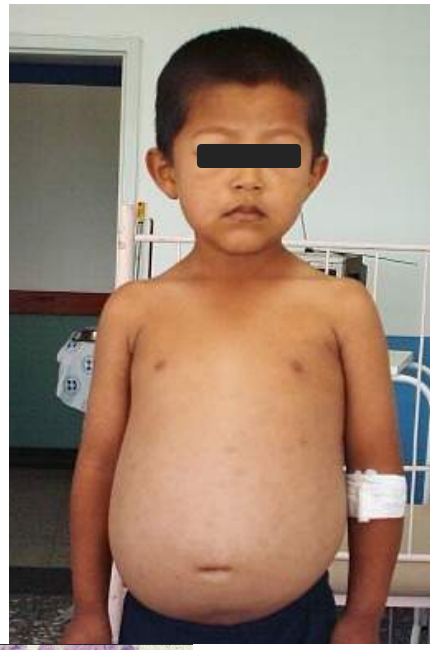
Principal causa de doença glomerular em pediatria.

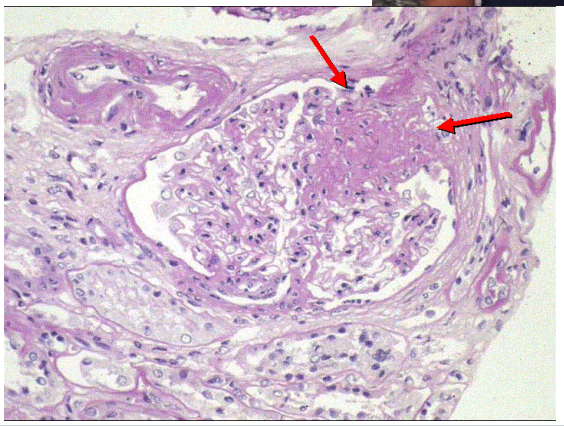
Síndrome nefrótica por lesões mínimas e Glomeruloesclerose focal e segmentar – espectros da mesma doença?

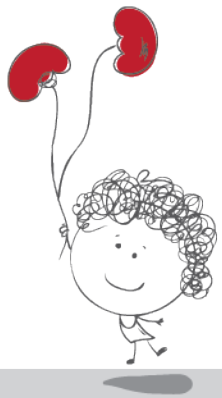
Marcadores prognósticos.

Sistema imune e do SRA.

Dificuldades no tratamento.





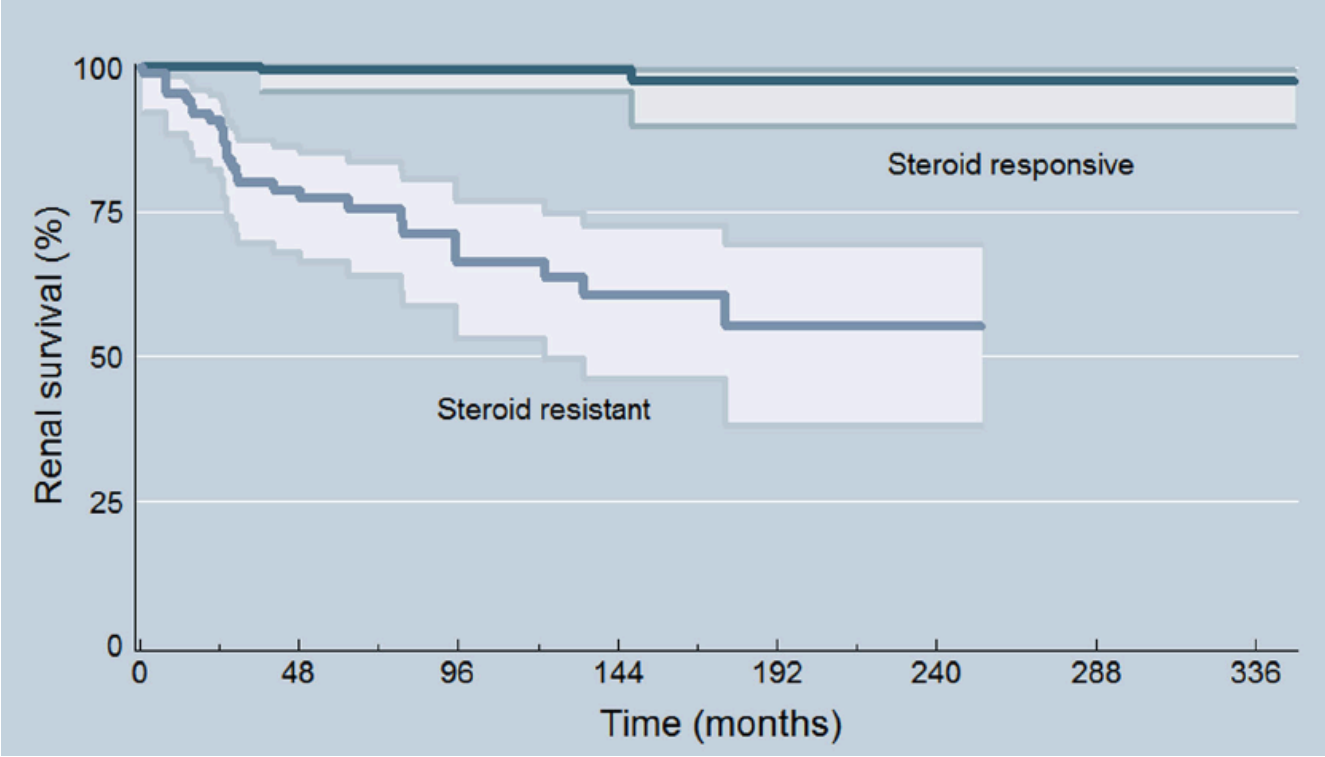


Pediatr Nephrol
DOI 10.1007/s00467-015-3136-0

ORIGINAL ARTICLE

A predictive model of progressive chronic kidney disease in idiopathic nephrotic syndrome

Ana Carmen Quaresma Mendonça[1] · Eduardo Araújo Oliveira[1] · Brunna Pinto Fróes[1] · Lauro Damasceno Carvalho Faria[2] · Juliana Silva Pinto[2] · Maira Melo Ibrahim Nogueira[2] · Gabriella Oliveira Lima[2] · Priscila Isa Resende[2] · Natália Silva Assis[2] · Ana Cristina Simões e Silva[1] · Sérgio Veloso Brant Pinheiro[1]



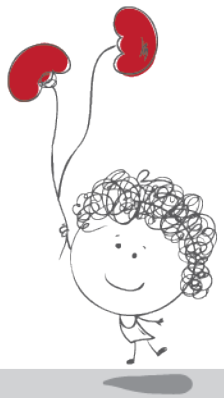
Pediatr Nephrol
DOI 10.1007/s00467-015-3136-0

ORIGINAL ARTICLE

A predictive model of progressive chronic kidney disease in idiopathic nephrotic syndrome

Ana Carmen Quaresma Mendonça[1] · Eduardo Araújo Oliveira[1] · Brunna Pinto Fróes[1] · Lauro Damasceno Carvalho Faria[2] · Juliana Silva Pinto[2] · Maira Melo Ibrahim Nogueira[2] · Gabriella Oliveira Lima[2] · Priscila Isa Resende[2] · Natália Silva Assis[2] · Ana Cristina Simões e Silva[1] · Sérgio Veloso Brant Pinheiro[1]

Variables	Coefficient	Hazard ratio (95% confidence interval)	*P* value	Score
Age at presentation (years)	0.157	1.17 (1.07–1.28)	<0.001	
1.0–3.0				0
3.1–6.0				1
6.1–9.0				2
9.1–12				3
12.1–15				4
Hematuria	1.19	3.30 (1.48–7.35)	0.003	
Absent				0
Present				2
Response to steroids	3.15	23.3 (5.43–100.3)	<0.001	
Steroid-sensitive				0
Steroid-resistant				7

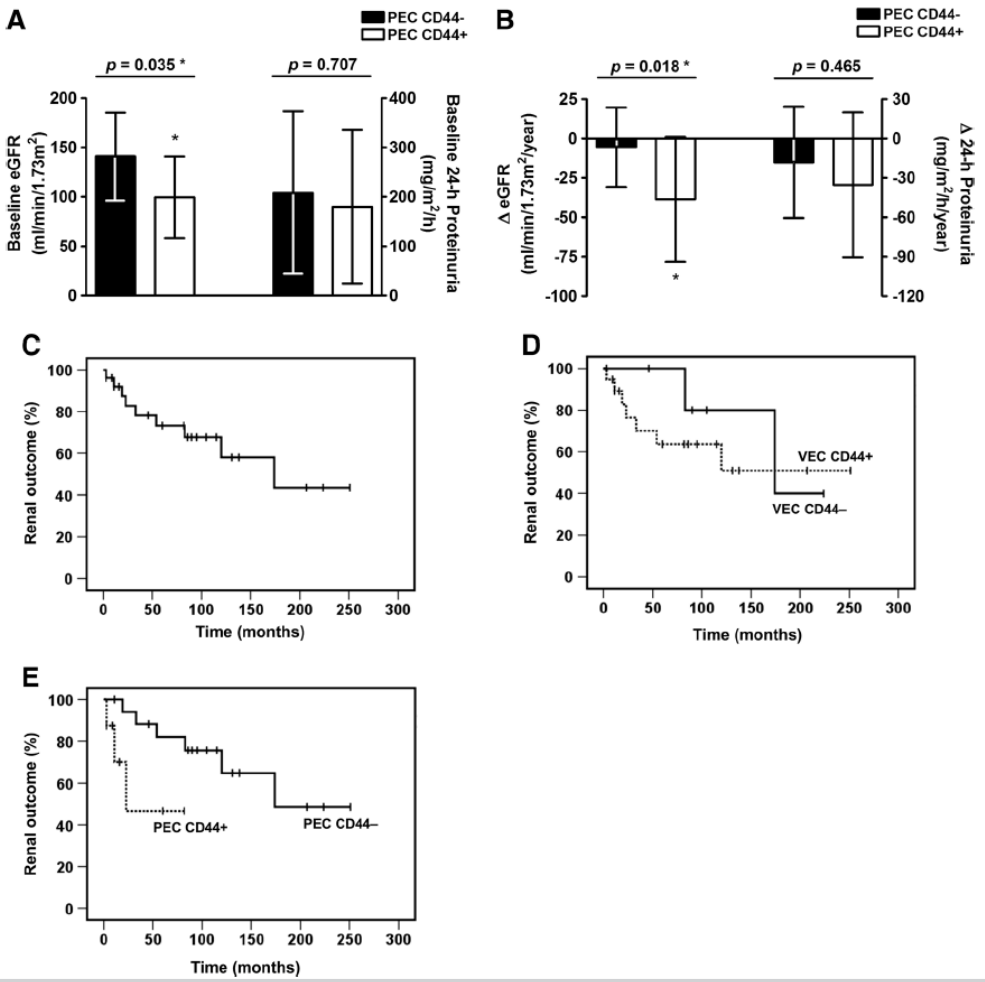


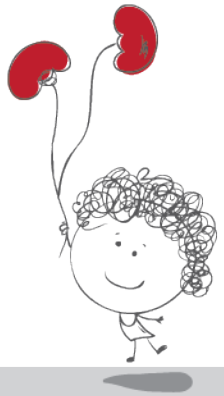
Pediatr Nephrol
DOI 10.1007/s00467-017-3775-4

BRIEF REPORT

Is CD44 in glomerular parietal epithelial cells a pathological marker of renal function deterioration in primary focal segmental glomerulosclerosis?

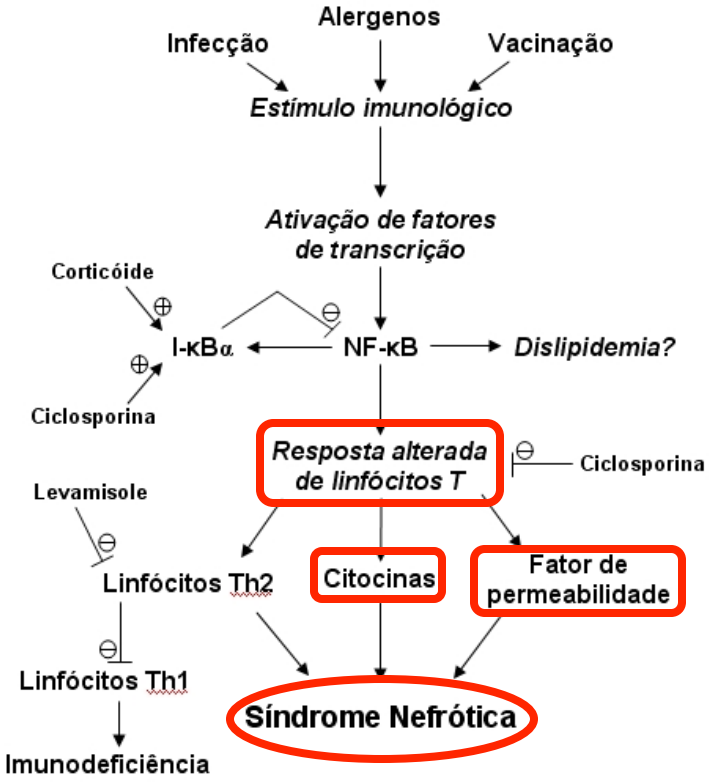
Brunna Pinto Froes[1] · Stanley de Almeida Araújo[2] · Eduardo Alves Bambirra[2] · Eduardo Araújo Oliveira[1] · Ana Cristina Simões e Silva[1,3] · Sérgio Veloso Brant Pinheiro[1]

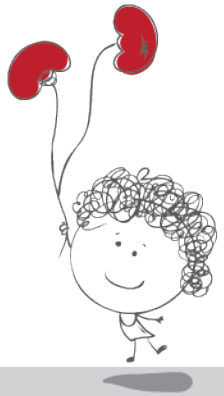




FISIOPATOLOGIA DA SÍNDROME NEFRÓTICA EM CRIANÇAS E ADOLESCENTES

Dres. Souto MFO[1]; Teixeira MM[2]; Penido MGMG[1]; Simões e Silva AC[1].



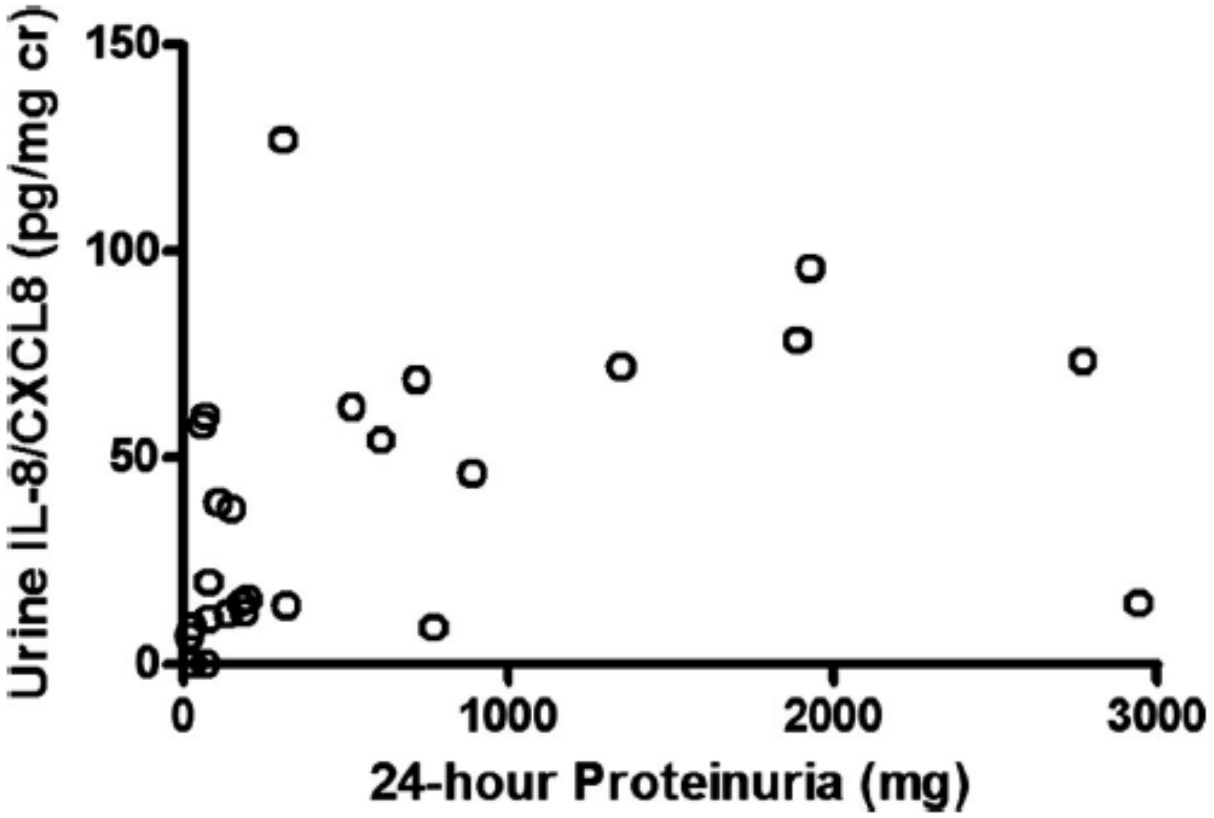


0031-3998/08/6406-0637
PEDIATRIC RESEARCH

Vol. 64, No. 6, 2008
Printed in U.S.A.

Immune Mediators in Idiopathic Nephrotic Syndrome: Evidence for a Relation Between Interleukin 8 and Proteinuria

MARCELO F. O. SOUTO, ANTÔNIO L. TEIXEIRA, REMO C. RUSSO, MARIA-GORETTI M. G. PENIDO, KÁTIA D. SILVEIRA, MAURO M. TEIXEIRA, AND ANA C. SIMÕES E SILVA



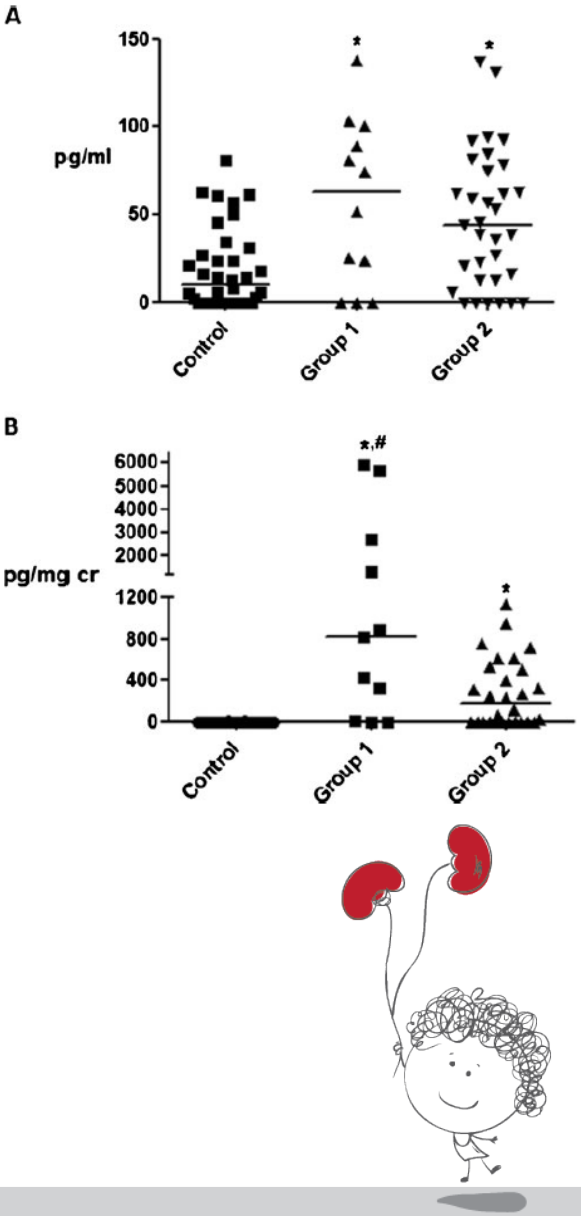
Pediatr Nephrol (2013) 28:463–469
DOI 10.1007/s00467-012-2363-x

ORIGINAL ARTICLE

Cytokines in chronic kidney disease: potential link of MCP-1 and dyslipidemia in glomerular diseases

Heloisa Reniers Vianna · Cristina Maria Bouissou M. Soares · Katia Daniela Silveira · Gustavo Siqueira Elmiro · Philipe Melgaço Mendes · Marcelo de Sousa Tavares · Mauro Martins Teixeira · Débora Marques Miranda · Ana Cristina Simões e Silva

Clinical, demographic, and laboratory parameters	Group 1 (n=11)	Group 2 (n=31)	Control (n=37)	p^b	p^c	p^d
Gender (male) (%)	45.4	77.4	56.8	0.040	0.062	0.119
Age (years)	12.9±1.0	11.7±1.3	11.5±0.8	0.580	0.350	0.900
eGFR[e] (ml/min/1.73 m^2)	54.9±13.1	47.9±5.2	128.0±6.0	0.551	<0.001	<0.001
Hemoglobin (g/dL)	12.0±2.1	12.3±1.5	–	0.512	–	–
Total cholesterol (mg/dL)	297±51	177±7	–	<0.001	–	–
Triglycerides (mg/dL)	199±58	109±9	–	0.019	–	–
Uric acid (mg/dL)	5.9±1.9	6.6±1.5	–	0.266	–	–
Phosphorus (mg/dL)	5.4±1.5	4.9±1.2	–	0.390	–	–
PTH (pg/ml)	147±35	108±17	–	0.275	–	–
Bicarbonate (mEq/L)	21.9±5.7	23.8±2.9	–	0.390	–	–
Serum albumin (g/dL)	3.1±0.3	4.3±0.1	–	<0.001	–	–
Hypertension (%)	5 (45.4)	6 (19.3)	None	0.090	–	–
Presence of proteinuria (%)	9 (81.8)	22 (70.9)	None	0.481	–	–
Use of RAS blockers (%)	9 (81.8)	11 (35.5)	None	0.008	–	–
Plasma MCP-1/CCL2 (pg/mL)	57.1±13.6	46.7±6.7	18.9±3.8	0.450	0.003	0.007
Plasma IL-8/CXCL8 (pg/mL)	0.82 0.06	1.75±0.14	Undetectable	0.801	–	–
Plasma TGF-β (pg/mL)	2.40±1.15	1.32±0.87	Undetectable	0.719	–	–
Urinary MCP-1/CCL2 (pg/mg cr)	1643.0±660.6	352.8±95.1	0.70±0.13	0.002	<0.001	<0.001
Urinary IL-8/CXCL8 (pg/mg cr)	25.6±17.5	110.3±57.4	Undetectable	0.666	–	–
Urinary TGF-β (pg/mg cr)	3.67±2.13	2.93±1.19	Undetectable	0.895	–	–



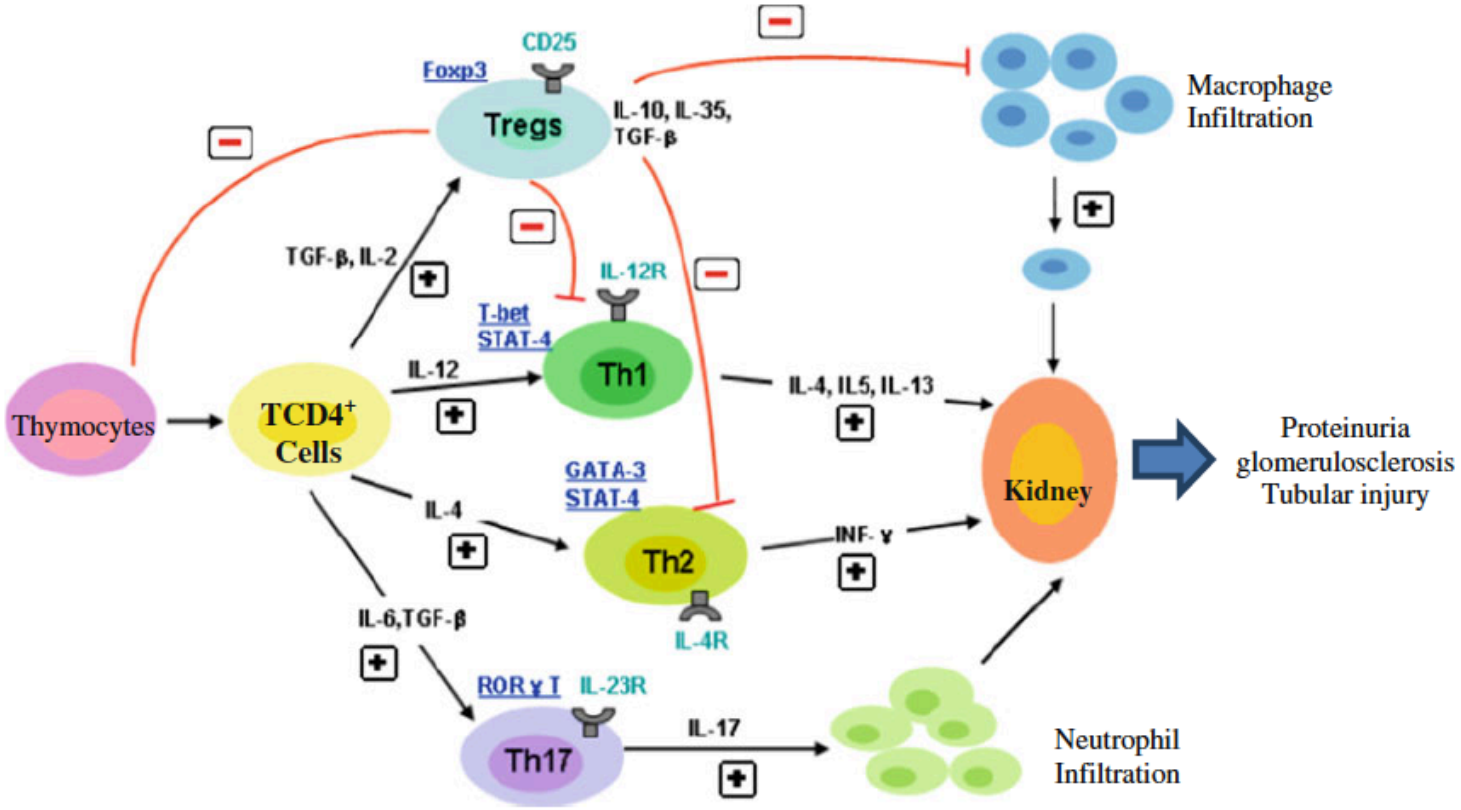
Inflamm. Res. (2014) 63:1–12
DOI 10.1007/s00011-013-0672-6

Inflammation Research

REVIEW

The role of the immune system in idiopathic nephrotic syndrome: a review of clinical and experimental studies

Wagner de Fátima Pereira · Gustavo Eustáquio Alvim Brito-Melo · Fábio Tadeu Lourenço Guimarães · Thiago Guimarães Rosa Carvalho · Elvis Cueva Mateo · Ana Cristina Simões e Silva



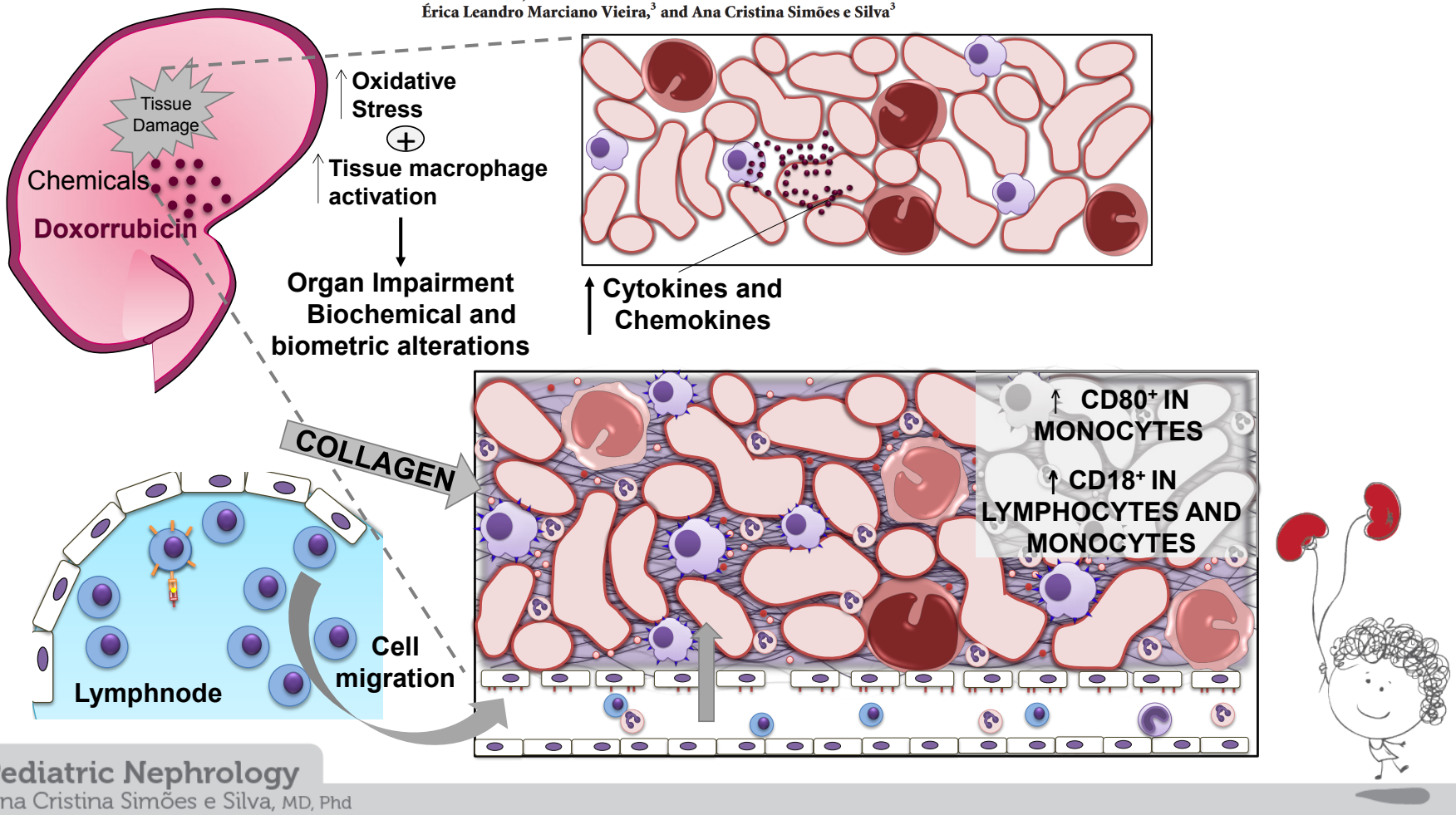
Hindawi Publishing Corporation
Mediators of Inflammation
Volume 2015, Article ID 209764, 11 pages
http://dx.doi.org/10.1155/2015/209764

Hindawi

Research Article

Increased Migratory and Activation Cell Markers of Peripheral Blood Lymphocytes in an Experimental Model of Nephrotic Syndrome

Wagner de Fátima Pereira,[1] Gustavo Eustáquio Alvim Brito-Melo,[1]
Cláudia Martins Carneiro,[2] Dirceu de Sousa Melo,[1] Karine Beatriz Costa,[1]
Fábio Lourenço Tadeu Guimarães,[1] Etel Rocha-Vieira,[1]
Érica Leandro Marciano Vieira,[3] and Ana Cristina Simões e Silva[3]



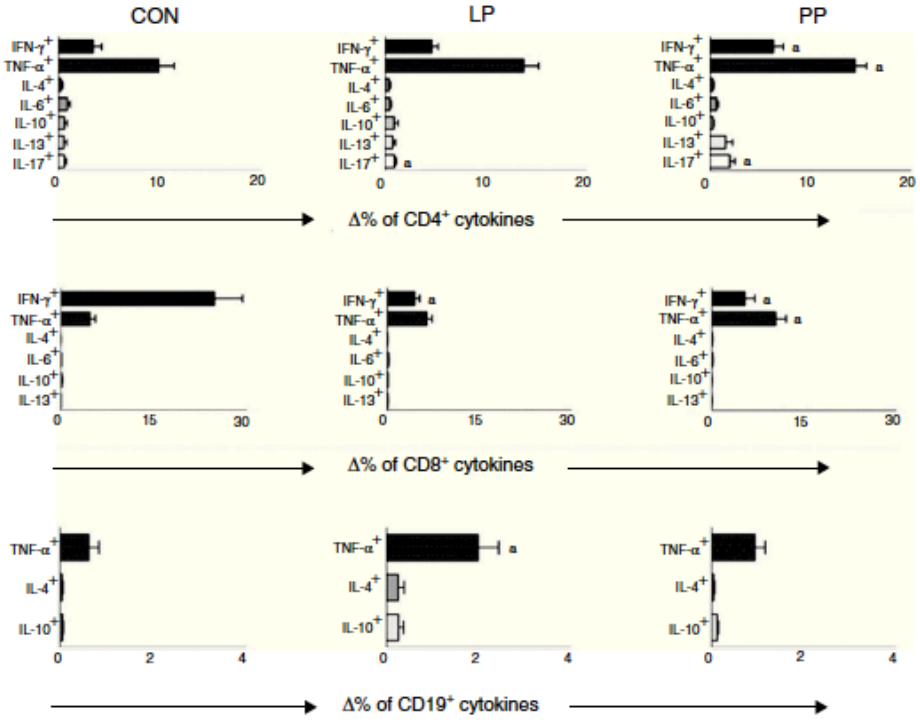
J Pediatr (Rio J). 2017;xxx(xx):xxx–xxx

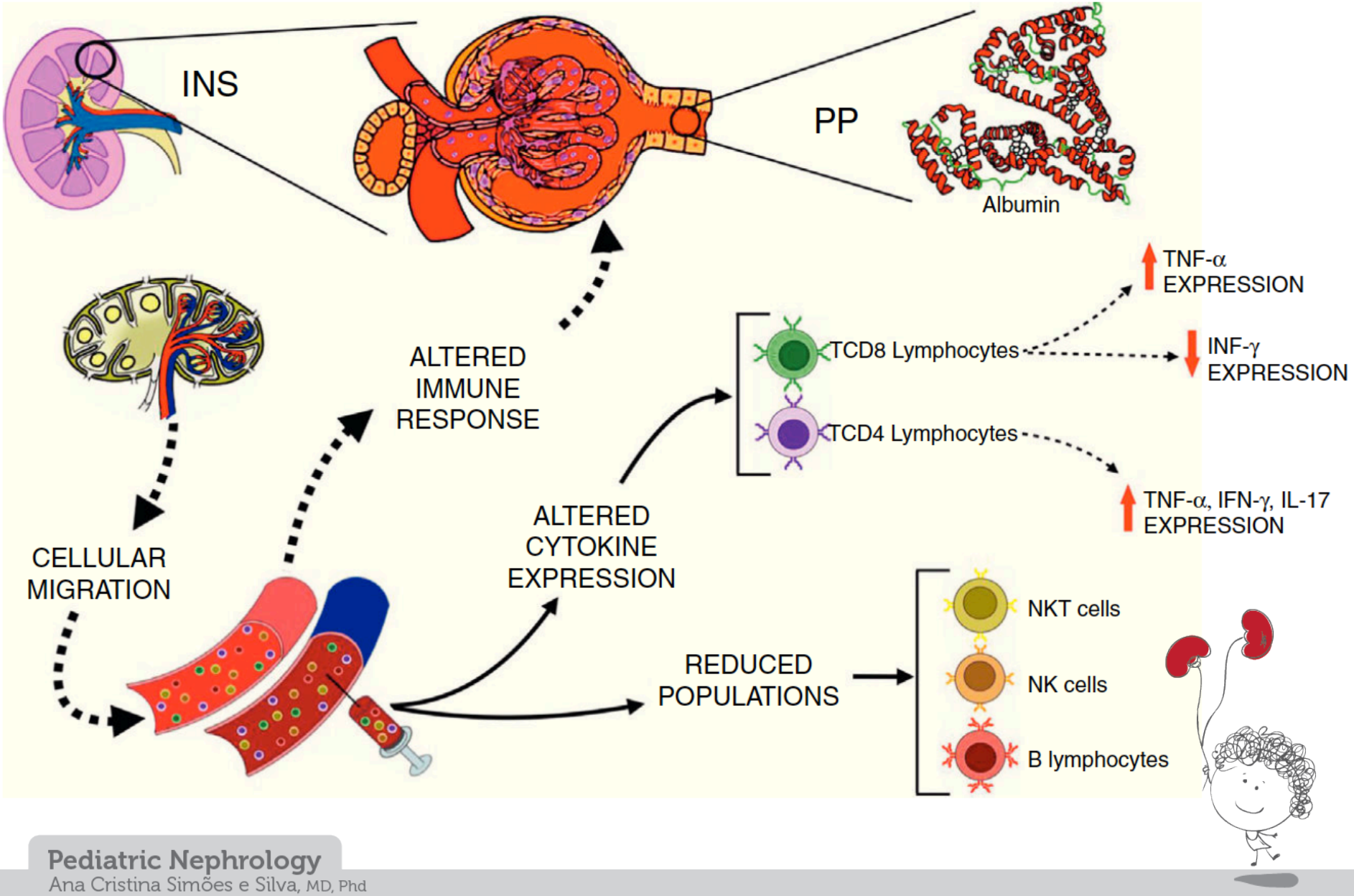
Jornal de Pediatria
www.jped.com.br

ORIGINAL ARTICLE

T-lymphocyte-expressing inflammatory cytokines underlie persistence of proteinuria in children with idiopathic nephrotic syndrome☆

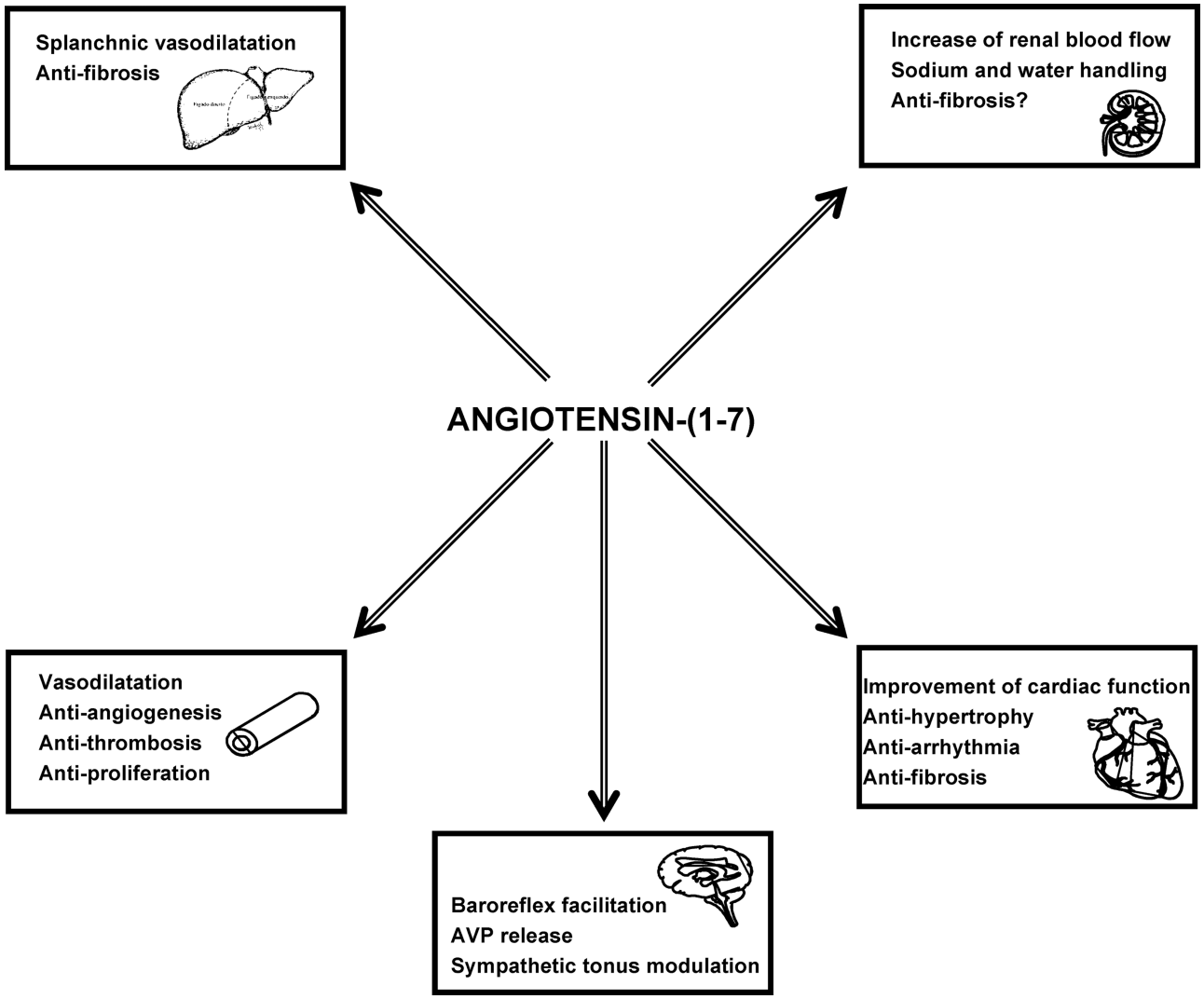
Fábio Tadeu Lourenço Guimarães[a], Gustavo Eustáquio Brito Alvim de Melo[a], Thiago Macedo Cordeiro[b], Victor Feracin[b], Etel Rocha Vieira[a], Wagner de Fátima Pereira[a], Sérgio Veloso Brant Pinheiro[b], Aline Silva Miranda[b,c], Ana Cristina Simões-e-Silva[b,*]




INS
PP
Albumin
TNF-α EXPRESSION
INF-γ EXPRESSION
TCD8 Lymphocytes
TCD4 Lymphocytes
TNF-α, IFN-γ, IL-17 EXPRESSION
ALTERED IMMUNE RESPONSE
ALTERED CYTOKINE EXPRESSION
CELLULAR MIGRATION
REDUCED POPULATIONS
NKT cells
NK cells
B lymphocytes

Sistema Renina Angiotensina

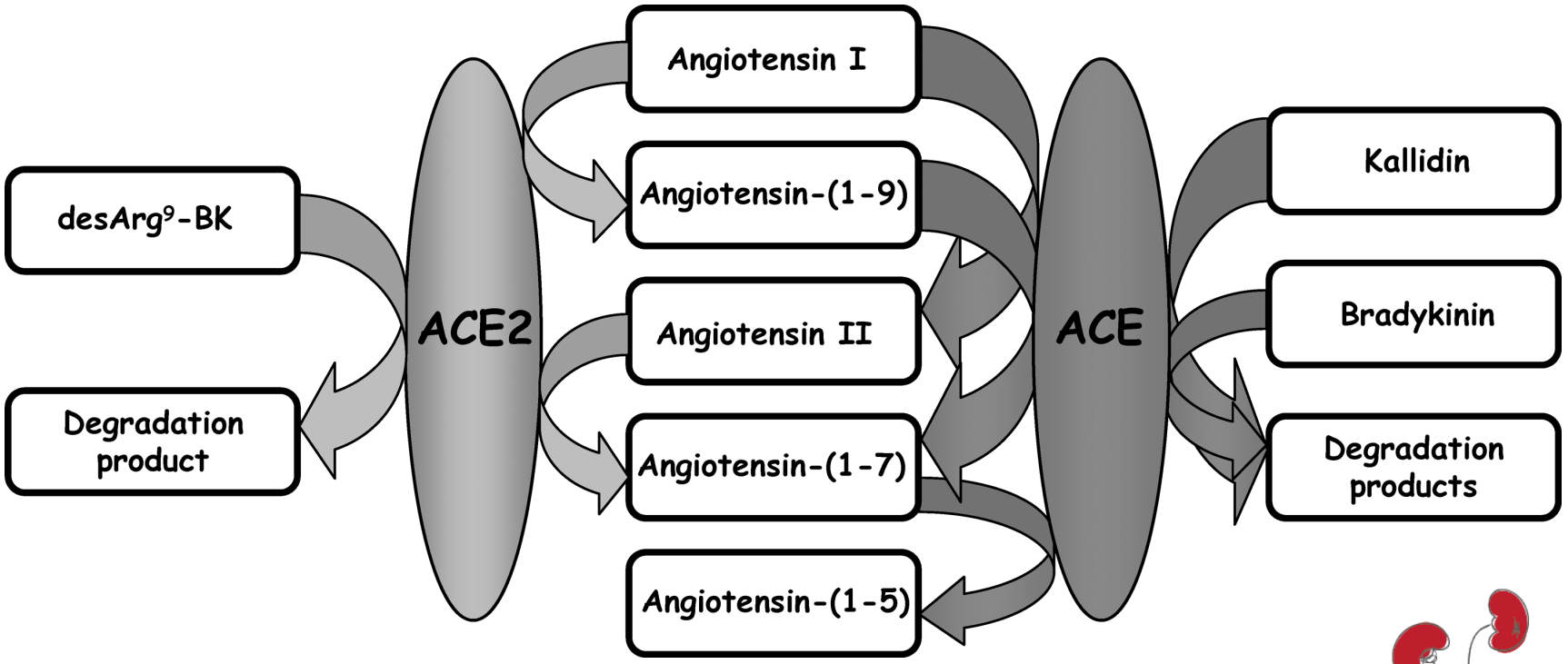
Pesquisa básica



Santos RAS, Ferreira AJ, Simões e Silva AC, Exp Physiol 2008; 93:519-27

Sistema Renina Angiotensina

Pesquisa básica



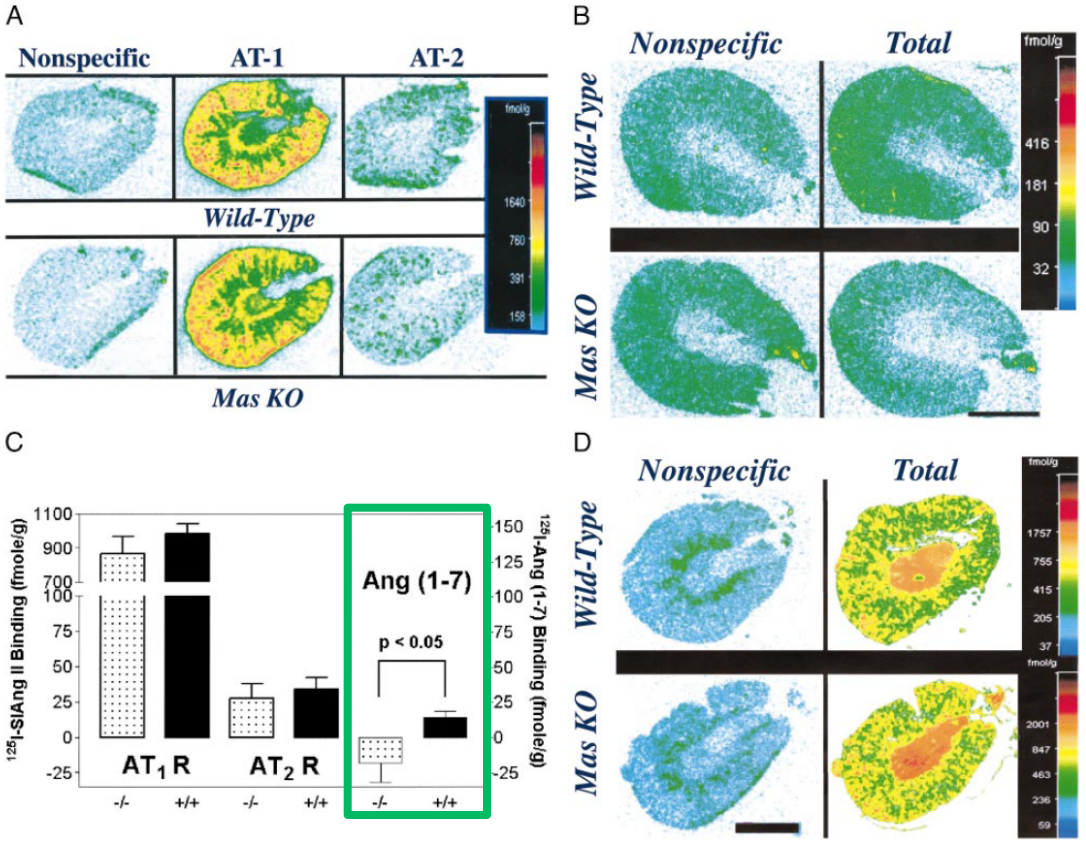
Santos RAS, Ferreira AJ, Simões e Silva AC, Exp Physiol 2008; 93:519-27

Sistema Renina Angiotensina

Pesquisa básica

Angiotensin-(1–7) is an endogenous ligand for the G protein-coupled receptor Mas

Robson A. S. Santos*, Ana C. Simoes e Silva*, Christine Maric†, Denise M. R. Silva*, Raquel Pillar Machado*, Insa de Buhr‡, Silvia Heringer-Walther‡, Sergio Veloso B. Pinheiro*, Myriam Teresa Lopes*, Michael Bader§, Elizabeth P. Mendes*, Virgina Soares Lemos*, Maria Jose Campagnole-Santos*, Heinz-Peter Schultheiss‡, Robert Speth¶‖, and Thomas Walther‡**



Santos RAS, Simoes e Silva AC, Maric C, et al, PNAS 2003; 100:8258-63

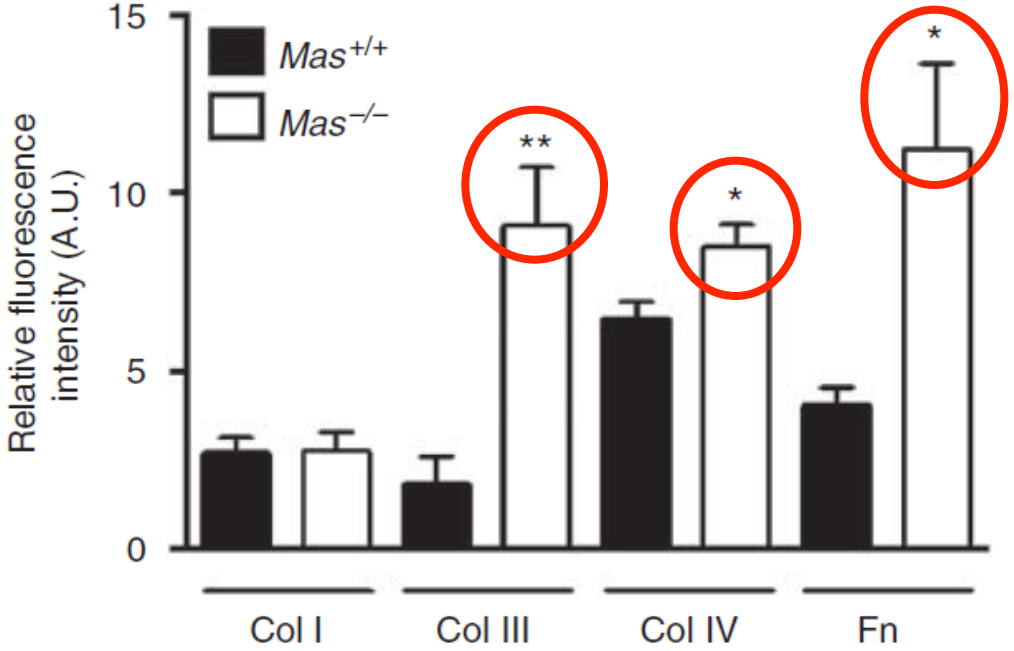
Sistema Renina Angiotensina

Pesquisa básica

original article http://www.kidney-international.org

Genetic deletion of the angiotensin-(1–7) receptor Mas leads to glomerular hyperfiltration and microalbuminuria

Sérgio V.B. Pinheiro[1], Anderson J. Ferreira[2], Gregory T. Kitten[2], Kátia D. da Silveira[3], Deivid A. da Silva[1], Sérgio H.S. Santos[3], Elisandra Gava[2], Carlos H. Castro[3], Júnio A. Magalhães[3], Renata K. da Mota[2], Giancarla A. Botelho-Santos[3], Michael Bader[4], Natalia Alenina[4], Robson A.S. Santos[3] and Ana Cristina Simoes e Silva[1]



Pinheiro SVB et al. Kidney Int 2009; 75:1184-93

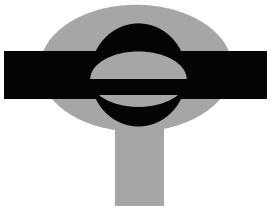
Sistema Renina Angiotensina

Pesquisa básica

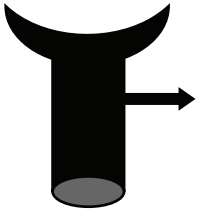
ACE-Ang II-AT_1
Fibrosis
Apoptosis
Inflammation
Na/H_2O retention

ACE2-Ang-(1-7)-Mas
Antifibrotic
Antiapoptotic
Anti-inflammatory
Na/H_2O homeostasis

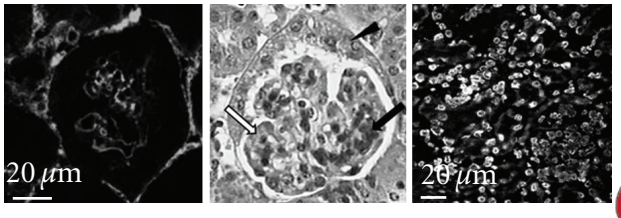
Renal RAS imbalance



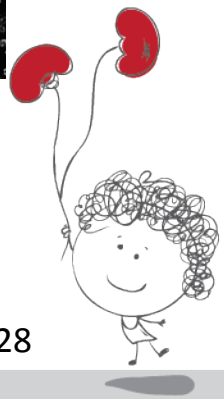
Glomerular hyperfiltration
↑ Proteinuria



Antidiuresis
↑ Na reabsorption



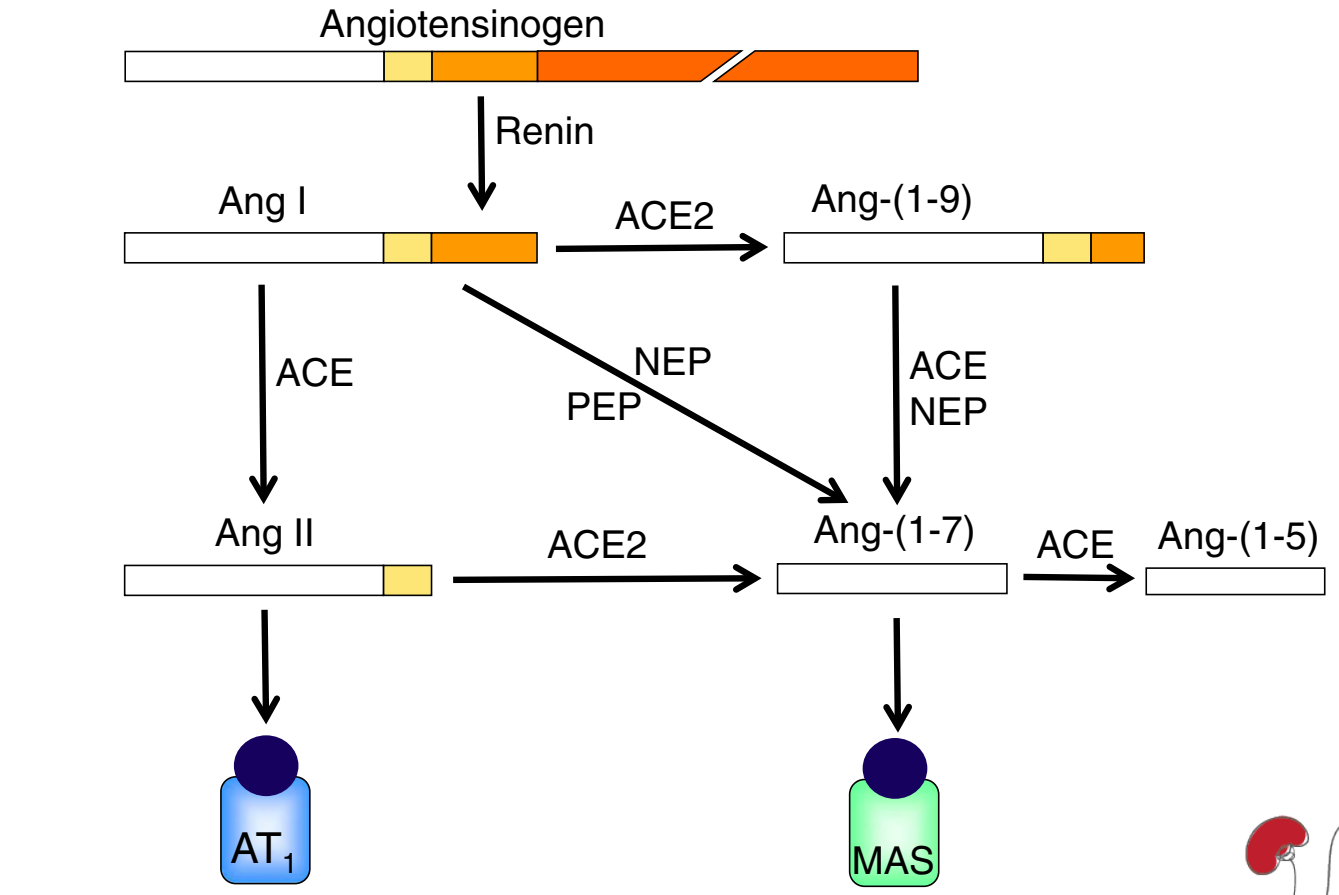
Matrix protein deposition
Interstitial fibrosis
Glomerulosclerosis
Apoptosis



Pinheiro SVB & Simões e Silva AC, Int J Hypertens 2012; Article ID 414128

Sistema Renina Angiotensina

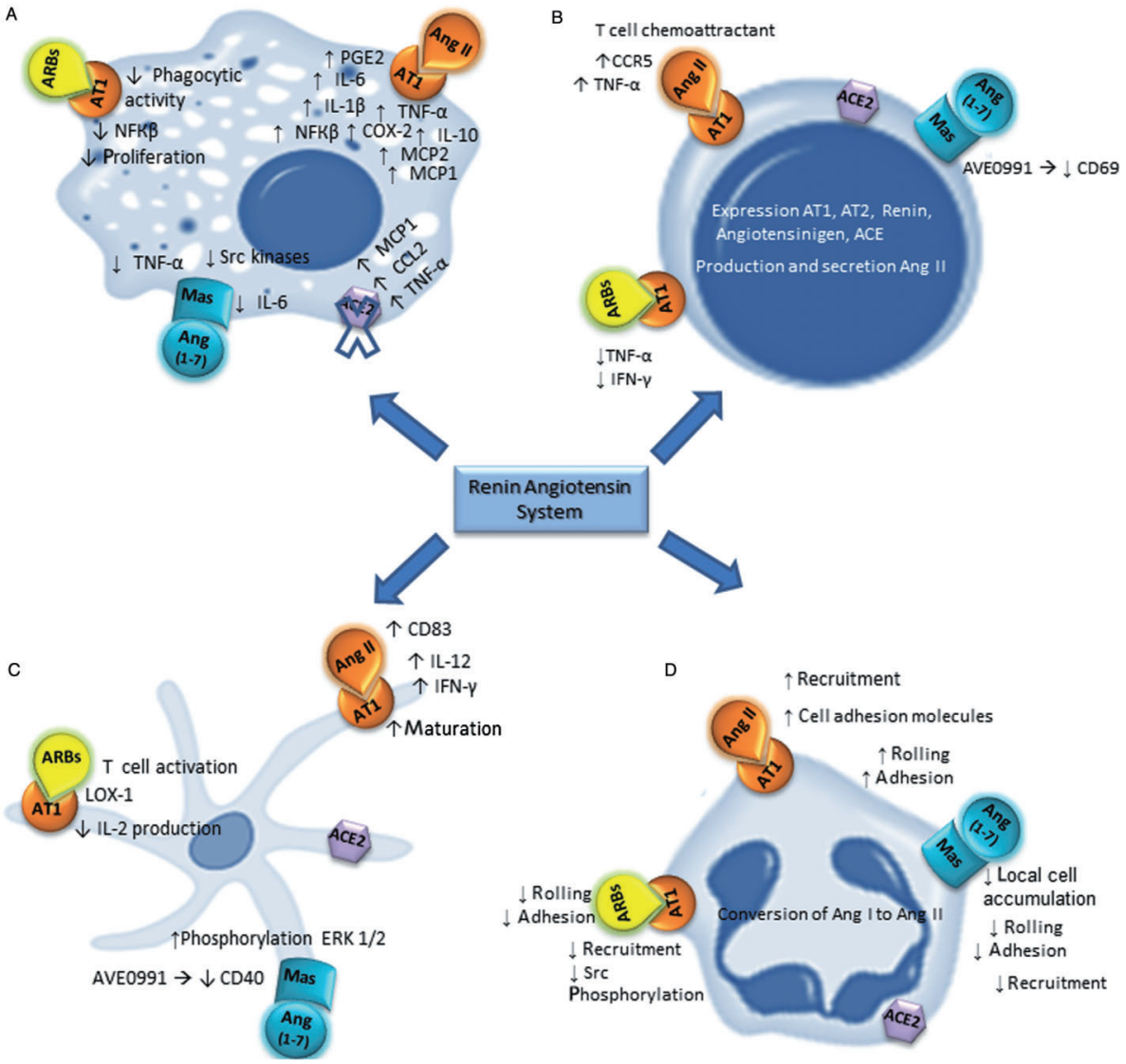
Aplicabilidade potencial



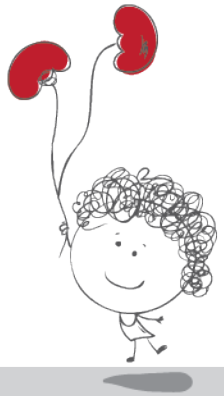
Simões e Silva & Flynn, Pediatr Nephrol 2012; 27:1835-45

Síndrome Nefrótica Primária

Perspectivas terapêuticas



Simões e Silva AC et al, British J Pharmacol 2013; 169:477-92



Síndrome Nefrótica Primária

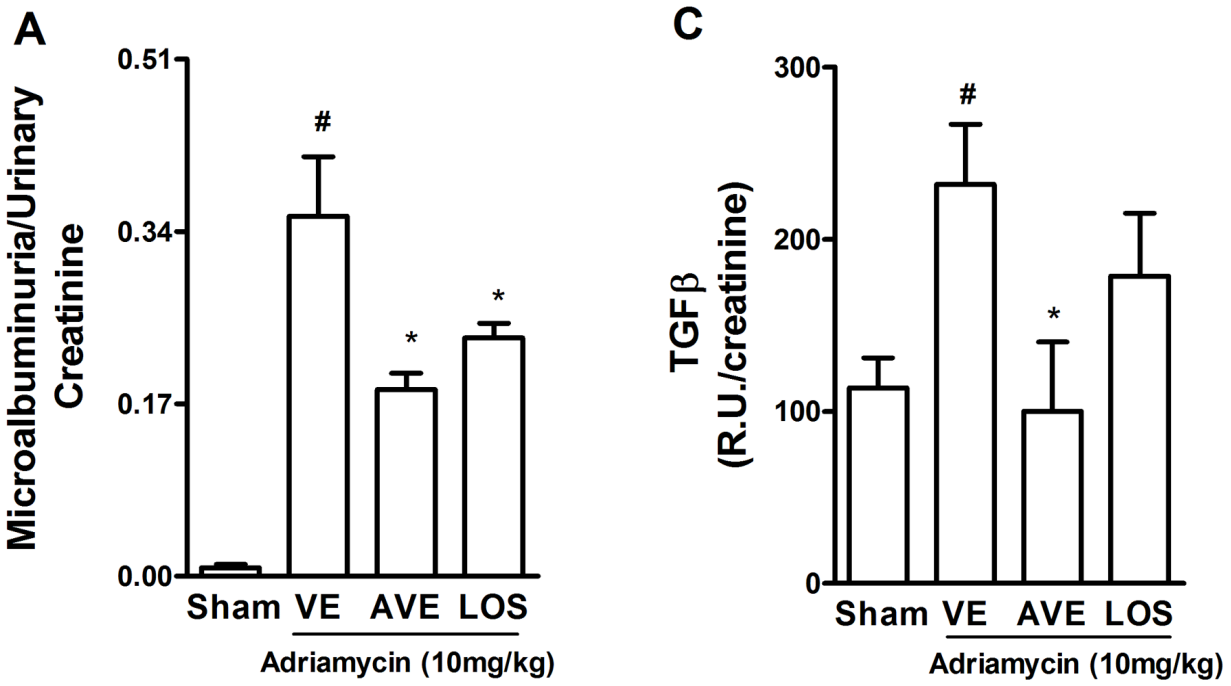
Perspectivas terapêuticas

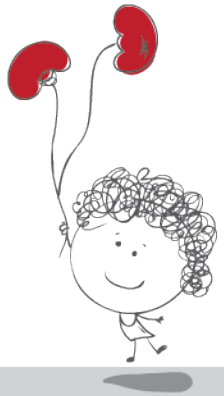
OPEN ACCESS Freely available online

PLOS ONE

Beneficial Effects of the Activation of the Angiotensin-(1–7) Mas Receptor in a Murine Model of Adriamycin-Induced Nephropathy

Kátia Daniela Silveira[1], Lívia Corrêa Barroso[1], Angélica Thomáz Vieira[1], Daniel Cisalpino[1], Cristiano Xavier Lima[1,3], Michael Bader[5], Rosa Maria Esteves Arantes[2], Robson Augusto Souza dos Santos[4], Ana Cristina Simões-e-Silva[3*], Mauro Martins Teixeira[1,3*]

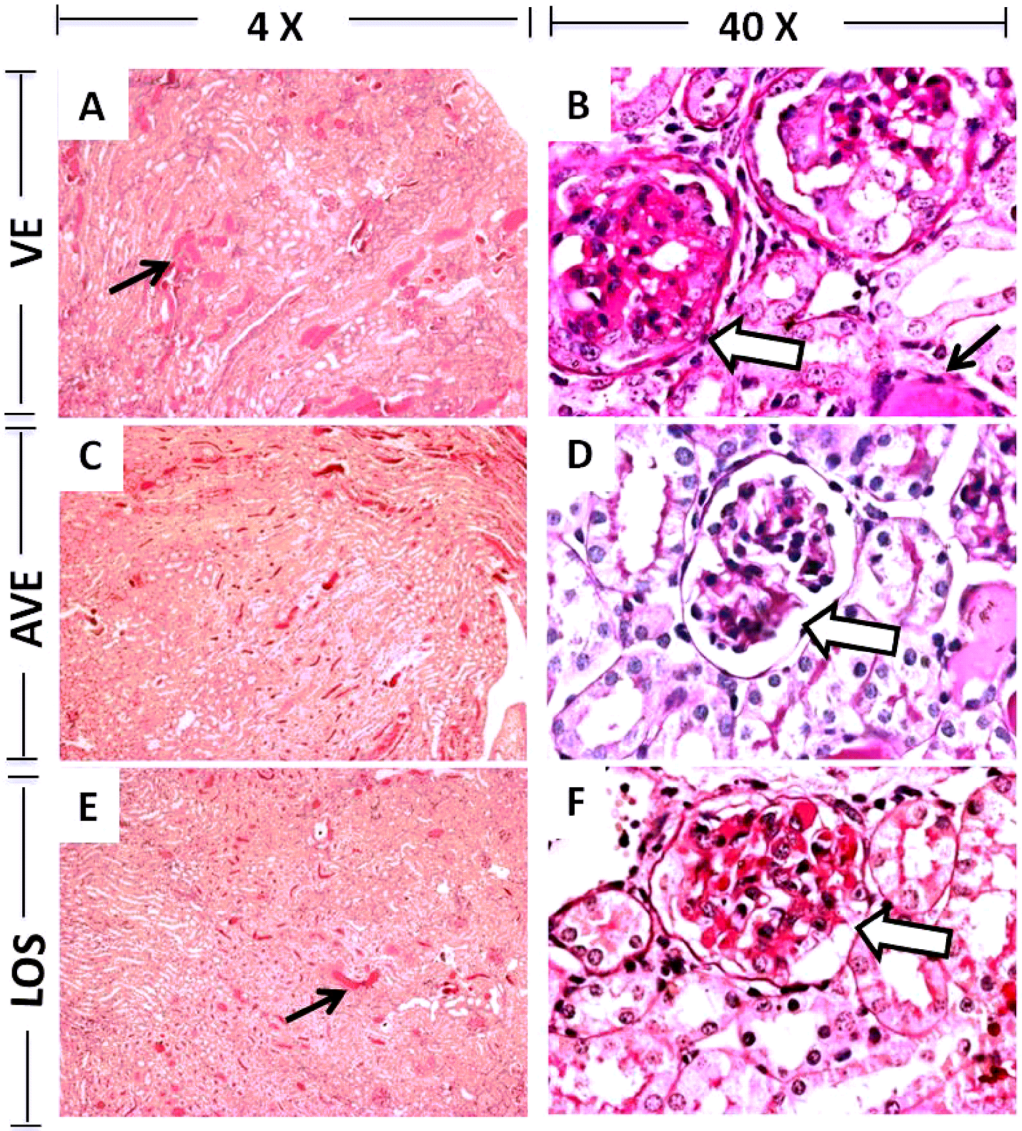


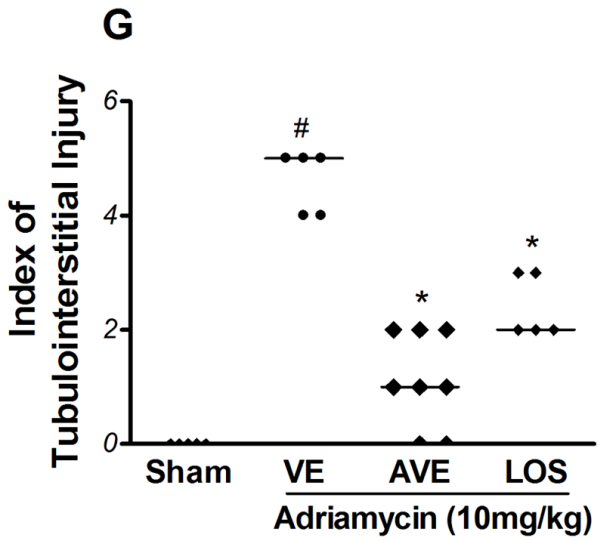


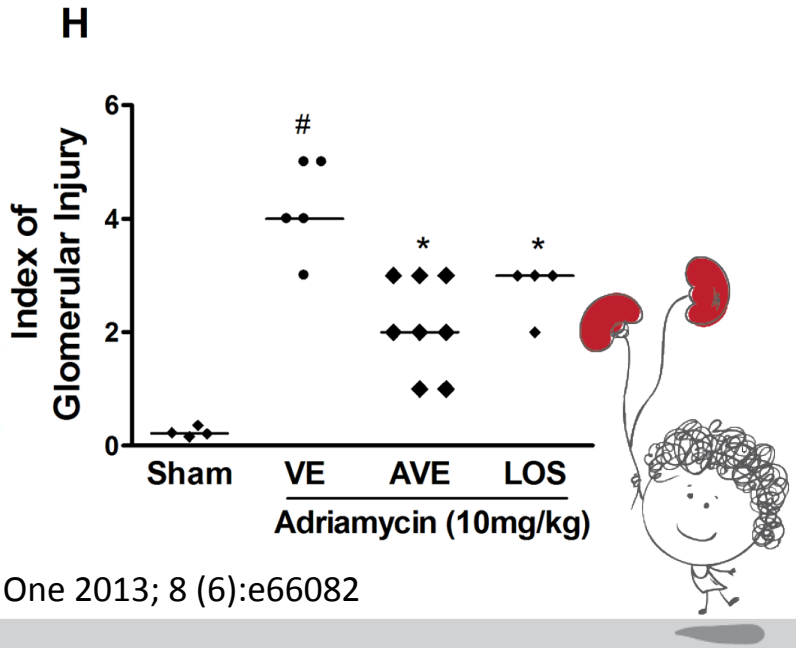
Silveira KD et al, Plos One 2013; 8 (6):e66082

Síndrome Nefrótica Primária

Perspectivas terapêuticas



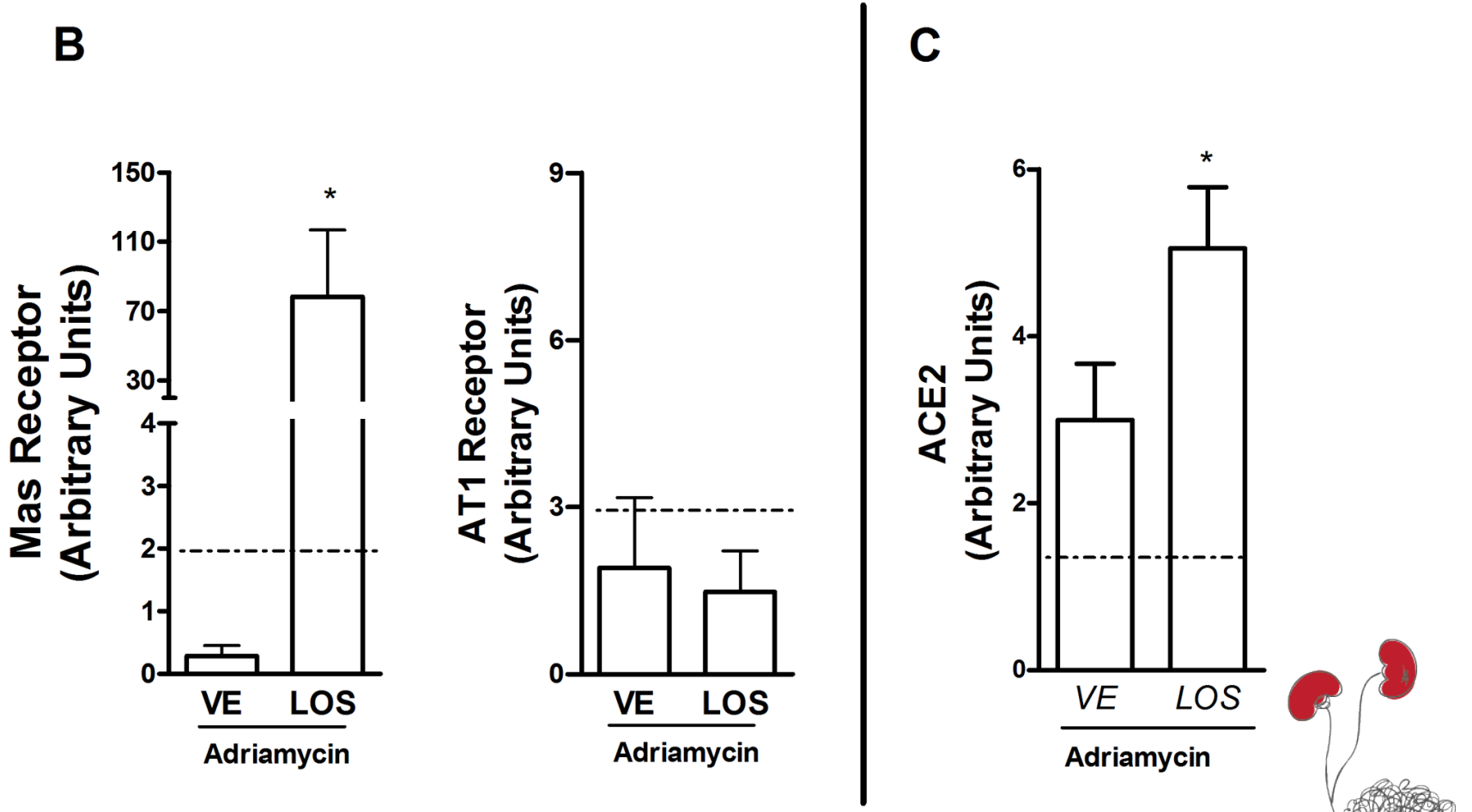




Silveira KD et al, Plos One 2013; 8 (6):e66082

Síndrome Nefrótica Primária

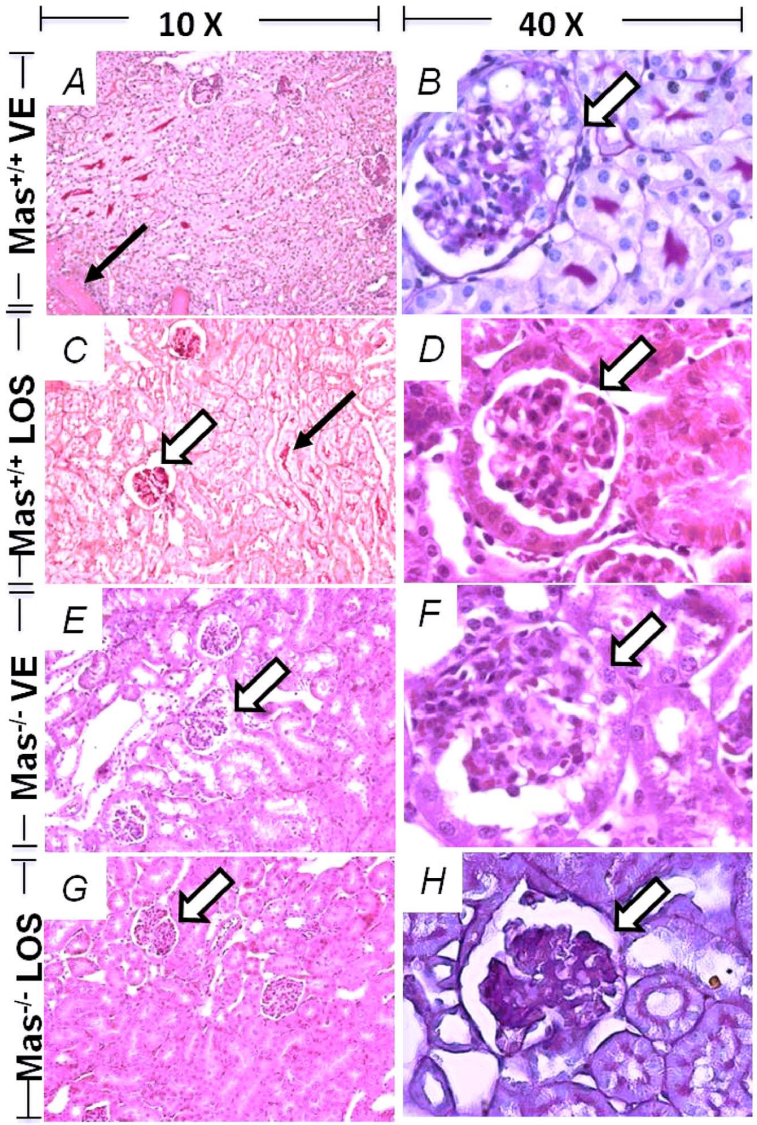
Perspectivas terapêuticas

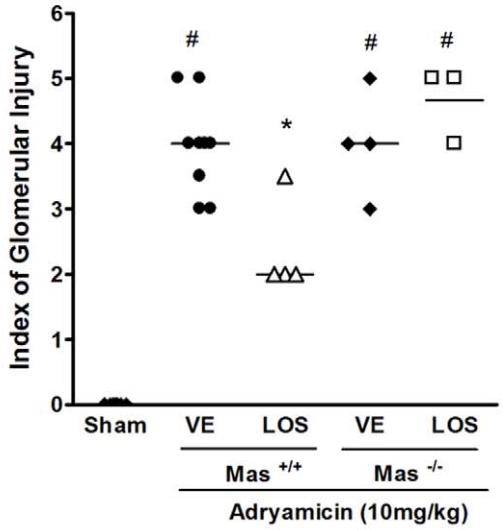


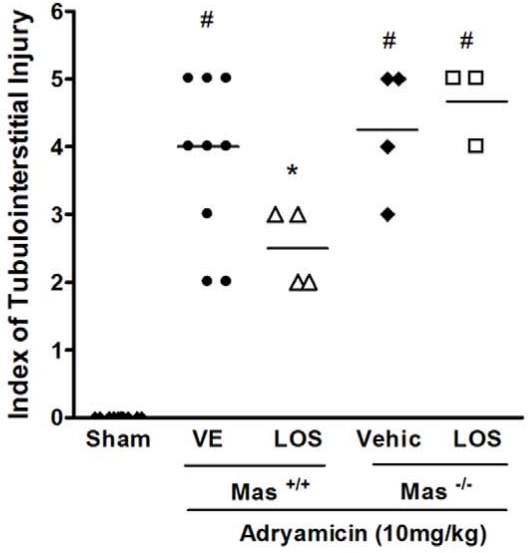
Silveira KD et al, Plos One 2013; 8 (6):e66082

Síndrome Nefrótica Primária

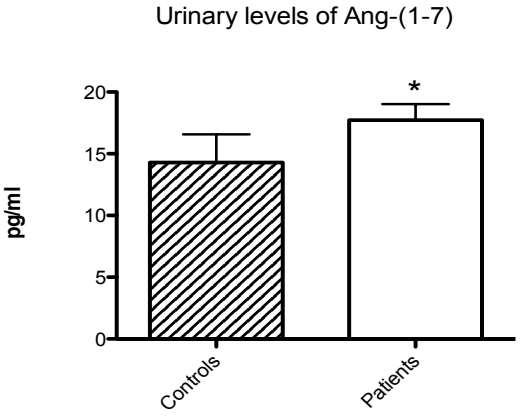
Perspectivas terapêuticas

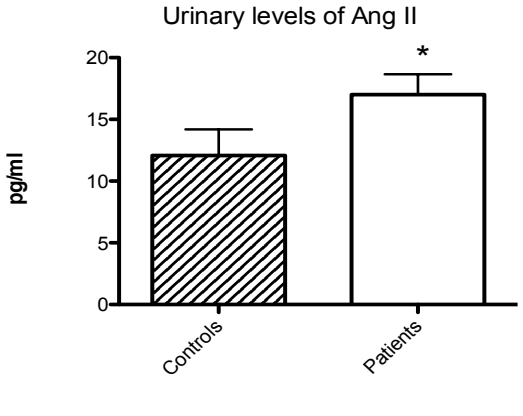


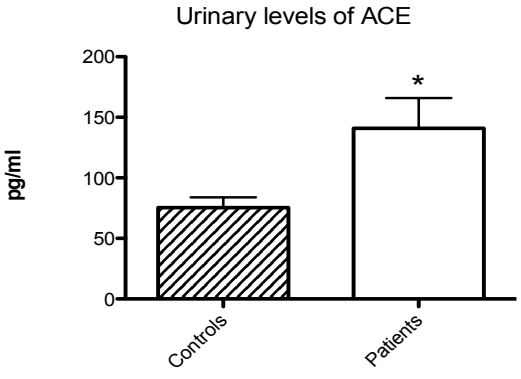


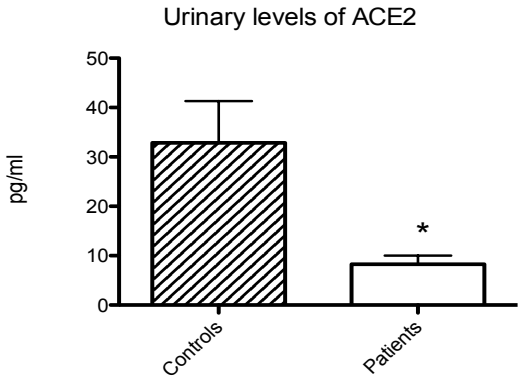


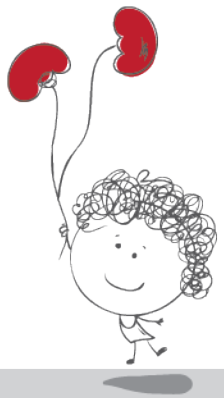
Silveira KD et al, Plos One 2013; 8 (6):e66082


Urinary levels of Ang-(1-7)
pg/ml
20
15
10
5
0
*
Controls
Patients


Urinary levels of Ang II
pg/ml
20
15
10
5
0
*
Controls
Patients


Urinary levels of ACE
pg/ml
200
150
100
50
0
*
Controls
Patients


Urinary levels of ACE2
pg/ml
50
40
30
20
10
0
*
Controls
Patients



	Proteinúria ausente	Proteinúria presente	p
Ang II	16,4 ± 8,4	14,7 ± 8,0	0,570
ECA I	98,4 ± 50,0	172,9 ± 162,2	0,247
Ang 1-7	17,5 ± 7,5	16,0 ± 6,8	0,662
ECA II	13,5 ±10,7	2,9 ± 5,2	0,023

Quimiocinas	***SRA***	**n**	**r**	**p**
IP-10	ECA 2	31	-0,4205	0,0185
MCP-1	Ang 1-7	31	-0,4850	0,0057
MIG	Ang 1-7	31	-0,3796	0,0352

	Proteinúria ausente	Proteinúria presente	p
Ang II	16,4 ± 8,4	14,7 ± 8,0	0,570
ECA I	98,4 ± 50,0	172,9 ± 162,2	0,247
Ang 1-7	17,5 ± 7,5	16,0 ± 6,8	0,662
ECA II	13,5 ±10,7	2,9 ± 5,2	0,023

Quimiocinas	***SRA***	**n**	**r**	**p**
IP-10	ECA 2	31	-0,4205	0,0185
MCP-1	Ang 1-7	31	-0,4850	0,0057
MIG	Ang 1-7	31	-0,3796	0,0352

Síndrome nefrótica primária

Papel de quimiocinas na síndrome nefrótica primária: IL-8 associada a alteração da permeabilidade glomerular (proteinúria) e MCP-1 associada à dislipidemia.

Aumento da atividade migratória de linfócitos e monócitos em modelo experimental de síndrome nefrótica e aumento de marcadores inflamatórios em pacientes recidivados.

Tratamento da síndrome nefrótica experimental com agonista oral do receptor Mas melhora a proteinúria, diminui a fibrose e a lesão histológica renal.

Diminuição de ECA2 nos pacientes com proteinúria persistente.

Interação do SRA com moléculas inflamatórias na SN.

Malformações dos rins e do trato urinário

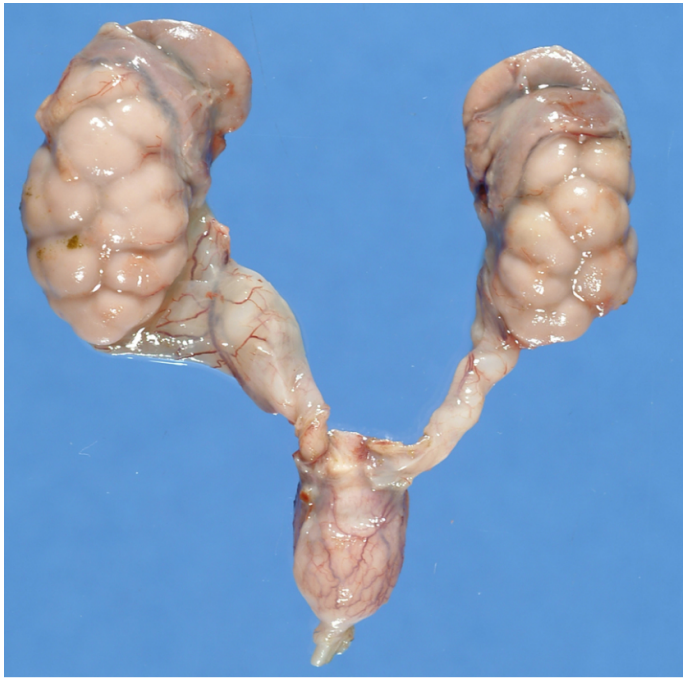
Causa muito frequente de malformação fetal.

Causa mais comum de DRC em crianças no nosso meio.

Faltam marcadores genéticos, moleculares, clínicos e de imagem capazes de predizer a evolução da função renal.

Importância de evitar a progressão da lesão renal.

Dificuldades na definição do tratamento.



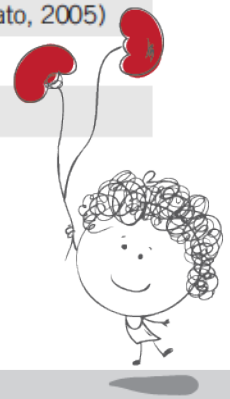
BIRTH DEFECTS RESEARCH (PART C) 102:374–381 (2014)

Congenital Anomalies of the Kidney and Urinary Tract: An Embryogenetic Review

Augusto Cesar Soares dos Santos Junior[1], Debora Marques de Miranda[1,2], and Ana Cristina Simões e Silva*[1,2]

TABLE 1. *Main Single-Gene Mutations Associated with Nonsyndromic Human CAKUT*

Gene	Phenotype	References
AGTR2	Ureteropelvic junction obstruction, megaureter, multicystic dysplastic kidney, hydronephrosis, posterior urethral valves	(Nishimura et al., 1999; Oshima et al., 2001; Nakanishi and Yoshikawa, 2003; Hahn et al., 2005; Miranda et al., 2014)
BMP4	Renal hypodysplasia	(Miyazaki et al., 2000; Hoshino et al., 2008; Weber et al., 2008a; Chi et al., 2011; Paces-Fessy et al., 2012; Dos Reis et al., 2014)
EYA1	Branchio-oto-renal (BOR) syndrome	(Abdelhak et al., 1997)
PAX2	Hipoplasia renal, coloboma renal, Vesicoureteral reflux	(Dressler et al., 1993; Nakanishi and Yoshikawa, 2003; Dziarmaga et al., 2006; Chen et al., 2008; Harshman and Brophy, 2012; de Miranda et al., 2014)
SALL	Townes-Brocks Syndrome	(Nishinakamura et al., 2001; Nishinakamura and Takasato, 2005)
SIX1	Branchio-oto-renal (BOR) syndrome	(Ruf et al., 2004)
SIX5	Branchio-oto-renal (BOR) syndrome	(Hoskins et al., 2007)



J Pediatr (Rio J). 2014;90(1):58–64

Jornal de Pediatria
www.jped.com.br

ORIGINAL ARTICLE

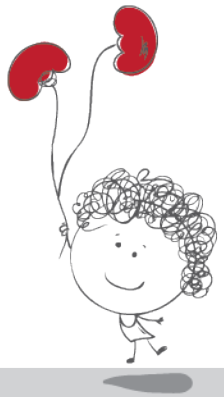
Study of the association between the BMP4 gene and congenital anomalies of the kidney and urinary tract☆

Geisilaine Soares dos Reis[a], Ana Cristina Simões e Silva[a,b,*], Izabella Silva Freitas[a], Thiago Ramos Heilbuth[a], Luiz Armando de Marco[a], Eduardo Araújo Oliveira[a,b], Débora Marques Miranda[a,b]

Table 1 Allelic, genotypic, and haplotypic frequencies and association between CAKUT patients and healthy controls.

Allele	Marker	Phenotype	Case	Control	OR	95% Lo	95% Hi	X^2	p-value[a]	p 1.000[b]
G	rs2071047	UPJO	0.60	0.45	1.00	1	1	4.98	0.03	0.16
A	rs2071047	UPJO	0.40	0.55	0.54	0.31	0.93	4.98	0.03	0.16
G	rs17563	UPJO	0.65	0.54	1.00	1	1	2.58	0.11	
A	rs17563	UPJO	0.36	0.46	0.64	0.37	1.11	2.58	0.11	
G	rs17563	VUR	0.56	0.54	1.00	1	1	0.06	0.79	
A	rs17563	VUR	0.44	0.45	0.94	0.58	1.52	0.07	0.79	
G	rs2071047	VUR	0.39	0.44	1.00	1	1	0.50	0.48	
A	rs2071047	VUR	0.60	0.56	1.19	0.73	1.94	0.50	0.48	
G	rs17563	Multicystic Kidney	0.44	0.46	1.00	1	1	0.09	0.76	
A	rs17563	Multicystic Kidney	0.56	0.54	1.08	0.65	1.81	0.09	0.76	
G	rs2071047	Multicystic Kidney	0.63	0.55	1.00	1	1	1.66	0.20	
A	rs2071047	Multicystic Kidney	0.37	0.45	0.71	0.42	1.19	1.66	0.20	
G	rs17563	All CAKUT phenotypes	0.36	0.46	1.00	1.00	1.00	9.10	0.002	0.54
A	rs17563	All CAKUT phenotypes	0.64	0.54	1.49	1.15	1.93	9.10	0.002	0.54
G	rs2071047	All CAKUT phenotypes	0.55	0.55	1.00	1.00	1.00	0.002	0.96	
A	rs2071047	All CAKUT phenotypes	0.45	0.45	0.99	0.77	1.28	0.002	0.96	
GA	rs17563	Multicystic Kidney	0.33	0.54	0.43	0.16	1.09	5.05	0.02	0.03
GG	rs2071047	UPJO	0.40	0.18	1.00	1	1	7.46	0.006	0.18
AA	rs17563, rs2071047	UPJO	0.22	0.37	0.46	0.23	0.93	4.62	0.03	0.33
GG	rs17563, rs2071047	All CAKUT phenotypes	0.31	0.36	1.00	1.00	1.00	3.88	0.05	0.82
GA	rs17563, rs2071047	All CAKUT phenotypes	0.05	0.09	0.67	0.35	1.30	5.98	0.01	0.33
AG	rs17563, rs2071047	All CAKUT phenotypes	0.24	0.18	1.54	1.04	2.28	5.72	0.02	0.02

OR, odds-ratio; Lo, lower limit; Hi, hight limit.
The results were obtained by χ^2 = chi-squared tests.
[a] uncorrected p-values.
[b] p-values obtained post 1,000 permutations.



Mol Diagn Ther
DOI 10.1007/s40291-014-0096-1

ORIGINAL RESEARCH ARTICLE

PAX2 Polymorphisms and Congenital Abnormalities of the Kidney and Urinary Tract in a Brazilian Pediatric Population: Evidence for a Role in Vesicoureteral Reflux

Débora Marques de Miranda · Augusto César Soares dos Santos Júnior · Geisilaine Soares dos Reis · Izabella Silva Freitas · Thiago Guimarães Rosa Carvalho · Luiz Armando Cunha de Marco · Eduardo Araújo Oliveira · Ana Cristina Simões e Silva

Table 7 Comparison between genotype frequencies of *PAX2* polymorphisms in patients with vesicoureteral reflux and the control group

SNP	VUR	Control	*P* value
rs11190693			
AA	0.13	0.26	0.04*
AT	0.63	0.50	0.09
TT	0.23	0.22	0.92
rs4244341			
GG	0.77	0.61	0.03*
GT	0.23	0.32	0.18
TT	0.00	0.05	0.07
rs11190698			
AA	0.77	0.65	0.09
AC	0.21	0.28	0.26
CC	0.02	0.06	0.21

SNP single nucleotide polymorphisms, *VUR* vesicoureteral reflux

* *P* value <0.05

Key Points

This is the first study of *PAX2* gene polymorphisms in a Brazilian sample of congenital anomalies of the kidney and urinary tract patients.

PAX2 gene polymorphisms are associated with vesicoureteral reflux.

PAX2 gene polymorphisms are not associated with multicystic dysplastic kidney and ureteropelvic junction obstruction.

NEPHROLOGY

Nephrology **19** (2014) 714–720

Original Article

Association of angiotensin type 2 receptor gene polymorphisms with ureteropelvic junction obstruction in Brazilian patients

DEBORA M MIRANDA,[1,2] AUGUSTO CESAR DOS SANTOS JR,[1,2] HELENA C SARUBI,[1] LUCIANA BASTOS-RODRIGUES,[1] DANIELA VALADÃO ROSA,[1] IZABELLA S FREITAS,[1] LUIZ ARMANDO DE MARCO,[1] EDUARDO A OLIVEIRA[1,2] and ANA CRISTINA SIMÕES E SILVA[1,2]

Table 2 Genotype and allele frequency of AGTR2 polymorphisms in patients with ureteropelvic junction obstruction (UPJO) and controls

SNP name	Patients (55)		Controls (262)		*P*-value	Odds-R	95%CI
	n°	%	*n*°	%			
rs1403543/c.-95-29G>A							
GG	28	0.56	72	0.41	0.62	1	1–1
GA	6	0.12	58	0.33	0.41	0.62	0.19–1.90
AA	16	0.32	44	0.25	0.98	0.94	0.45–1.92
G	41	0.63	162	0.56	0.33	1	1–1
A	24	0.37	125	0.44		0.76	0.43–1.32
rs3736556/c.-36 + 55A>T							
AA	36	0.92	138	0.66	**0.02**	1	1–1
AT	2	0.05	48	0.24	0.21	0.33	0.07–1.59
TT	1	0.03	23	0.11	0.07	0.17	0.02–1.28
A	48	0.94	271	0.78	**0.01**	1	1–1
T	3	0.06	77	0.22		0.22	0.07–0.73
rs35474657/c.971G>A							
GG	55	1	262	1	1	1	1–1
G	71	1	431	1	1	1	1–1
rs5193/c.†199G>T							
GG	20	0.87	93	0.77	0.84	1	1–1
GT	1	0.04	19	0.16	0.69	0.64	0.07–5.88
TT	2	0.09	9	0.07	0.94	1.03	0.21–5.15
G	26	0.90	171	0.84	0.51	1	1–1
T	3	0.10	30	0.15		0.66	0.19–2.31
rs5194/c.†205A>G							
AA	5	0.20	22	0.31	0.09	1	1–1
AG	3	0.12	22	0.31	0.98	0.33	0.33–11.96
GG	17	0.68	28	0.39	0.11	0.85	0.85–8.38
A	8	0.25	59	0.48	**0.02**	1	1–1
G	24	0.75	65	0.52		2.72	1.14–6.53

†After a 1000 permutation, corrected best *P*-value > 0.05. Bold values are significant values of *P*.

Article

The Genomic Landscape of Congenital Anomalies of the Kidney and Urinary Tract

Miguel Verbitsky[1*], Rik Westland[1,2*], Alejandra Perez[1], Krzysztof Kiryluk[1], Qingxue Liu[1], Priya Krithivasan[1], Adele Mitrotti[1], David A. Fasel[1], Ekaterina Batourina[3], Matthew G. Sampson[4], Monica Bodria[5,6], Max Werth[1], Charlly Kao[7], Jeremiah Martino[1], Valentina P. Capone[1], Asaf Vivante[8], Shirlee Shril[8], Byum Hee Kil[1], Maddalena Marasa[1], Jun Y. Zhang[1], Young-Ji Na[1], Tze Y. Lim[1], Dina Ahram[1], Patricia L. Weng[9], Erin L. Einzen[10], Alba Carrea[5], Giorgio Piaggio[5], Loreto Gesualdo[11], Valeria Manca[12], Giuseppe Masnata[12], Maddalena Gigante[13], Daniele Cusi[14], Claudia Izzi[15], Francesco Scolari[16], Joanna A.E. van Wijk[2], Marijan Saraga[17,18], Domenico Santoro[19], Giovanni Conti[20], Pasquale Zamboli[21], Hope White[1], Dorota Drozdz[22], Katarzyna Zachwieja[22], Monika Miklaszewska[23], Marcin Tkaczyk[24], Daria Tomczyk[24], Anna Krakowska[24], Przemyslaw Sikora[25], Tomasz Jarmoliński[26], Maria K. Borszewska-Kornacka[27], Robert Pawluch[27], Maria Szczepanska[27], Piotr Adamczyk[27], Malgorzata Mizerska-Wasiak[28], Grazyna Krzemien[28], Agnieszka Szmigielska[28], Marcin Zaniew[29], Mark G. Dobson[30], John M. Darlow[30], Prem Puri[31], David E. Barton[32], Susan L. Furth[33], Bradley A. Warady[34], Zoran Gucev[35], Vladimir J. Lozanovski[35], Velibor Tasic[36], Isabella Pisani[6], Landino Allegri[6], Lida M. Rodas[37], Josep M. Campistol[37], Cecile Jeanpierre[38], Shumyle Alam[39], Pasquale Casale[39], Craig S. Wong[40], Fangming Lin[41], Débora M. Miranda[42], Eduardo A. Oliveira[42], Ana Cristina Simões-e-Silva[42], Jonathan M. Barasch[1], Brynn Levy[43], Nan Wu[44,45], Friedhelm Hildebrandt[8], Gian Marco Ghiggeri[5], Anna Latos-Bielenska[46], Anna Materna-Kiryluk[46], Feng Zhang[47], Hakon Hakonarson[7], Virginia E. Papaioannou[48$], Cathy L. Mendelsohn[3$], Ali G. Gharavi[1$], and Simone Sanna-Cherchi[1$]

Our ref: NG-A47314R1

7th Jun 2018

Dear Dr. Sanna-Cherchi,

Thank you for submitting your revised manuscript "The Genomic Landscape of Congenital Anomalies of the Kidney and Urinary Tract" (NG-A47314R1). The reviewers find that the paper has improved in revision, and therefore we will be happy in principle to publish it in Nature Genetics, pending minor revisions to comply with our editorial and formatting guidelines. At this stage, we will need the corresponding author to upload a copy of the manuscript in MS Word .docx or similar editable format if you have not already done so.

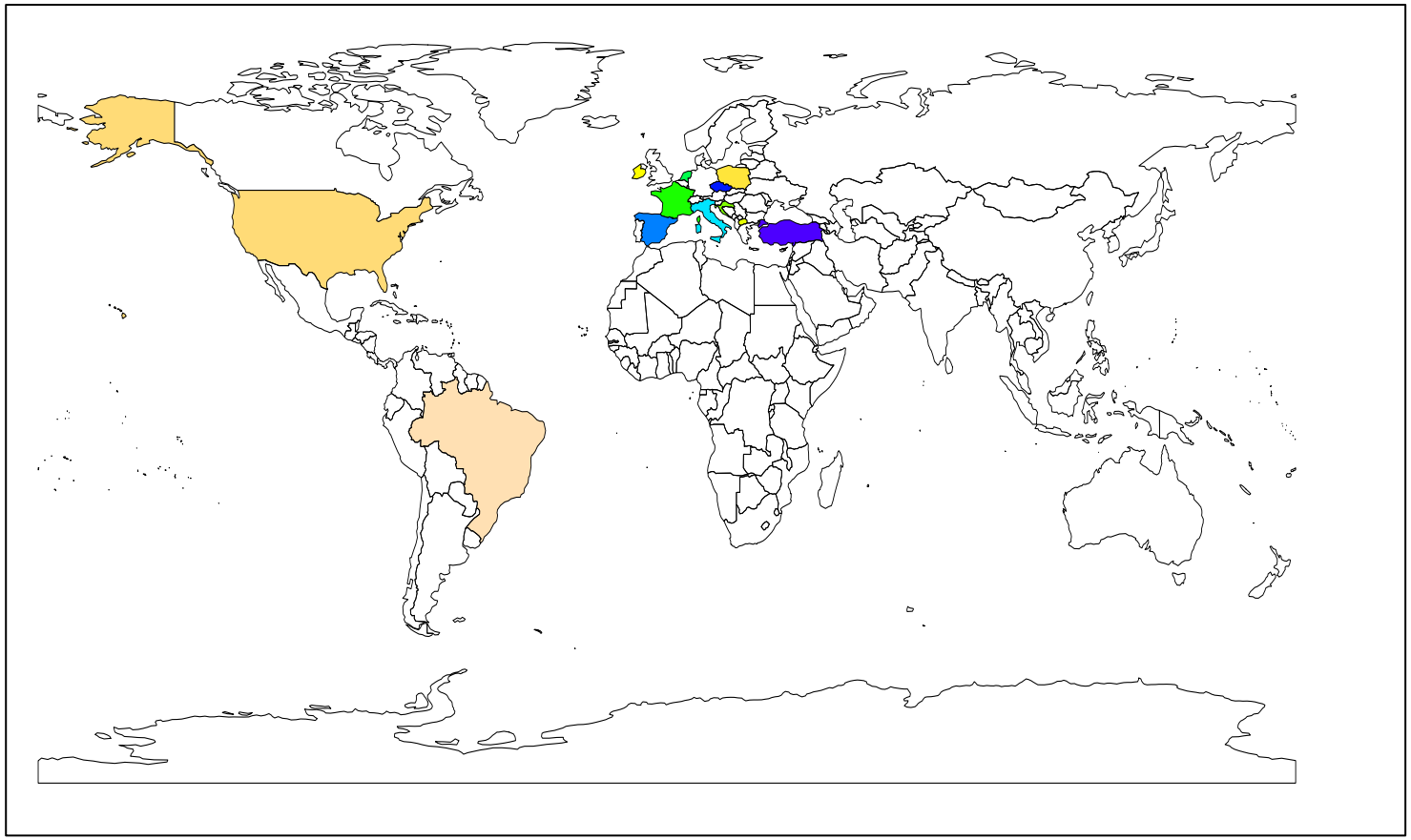


Figure 1

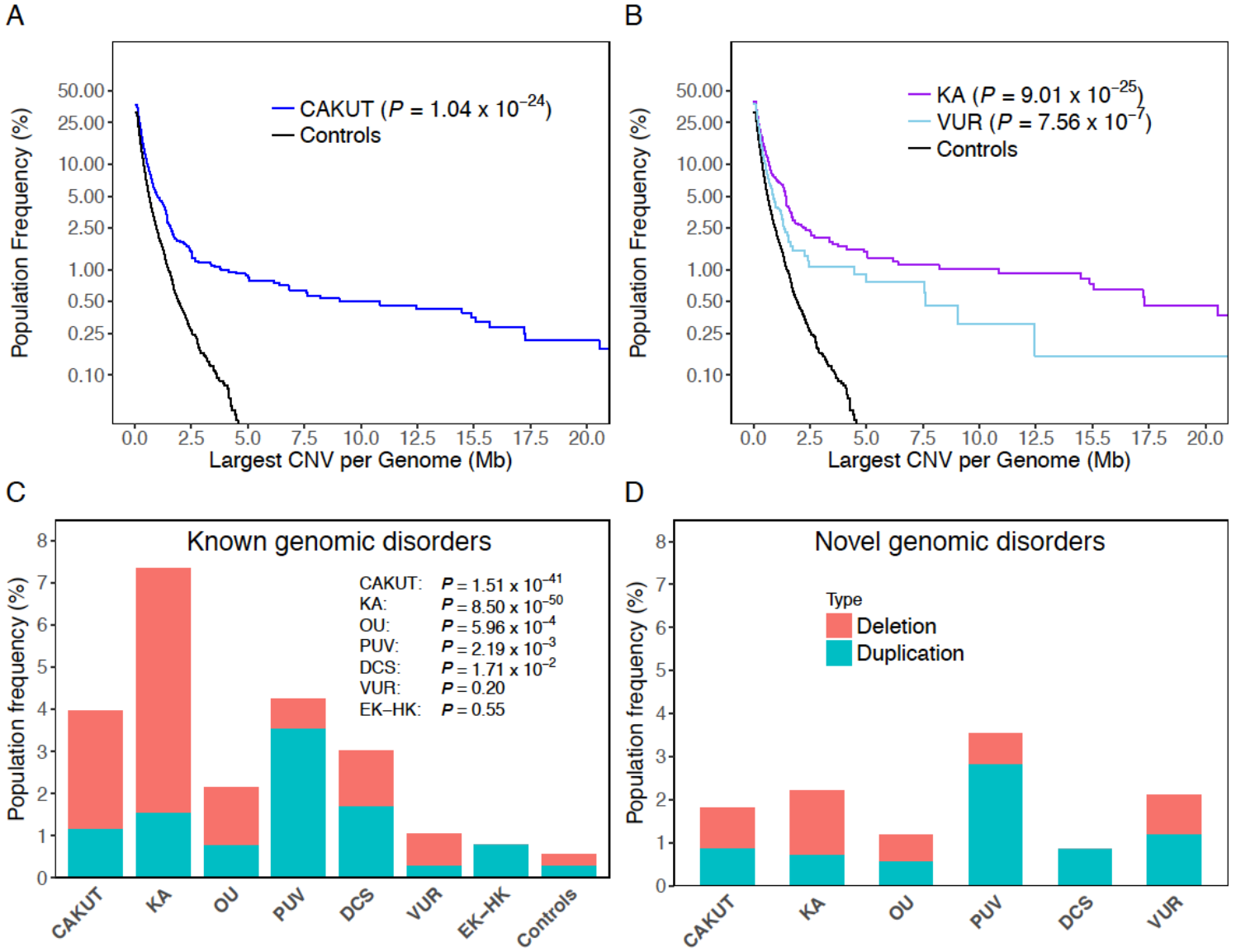

A
Population Frequency (%)
50.00
25.00
10.00
5.00
2.50
1.00
0.50
0.25
0.10
CAKUT (P = 1.04 x 10^{-24})
Controls
0.0 2.5 5.0 7.5 10.0 12.5 15.5 17.5 20.0
Largest CNV per Genome (Mb)
B
Population Frequency (%)
KA (P = 9.01 x 10^{-25})
VUR (P = 7.56 x 10^{-7})
Controls
Largest CNV per Genome (Mb)
C
Known genomic disorders
Population frequency (%)
CAKUT: P = 1.51 x 10^{-41}
KA: P = 8.50 x 10^{-50}
OU: P = 5.96 x 10^{-4}
PUV: P = 2.19 x 10^{-3}
DCS: P = 1.71 x 10^{-2}
VUR: P = 0.20
EK–HK: P = 0.55
CAKUT KA OU PUV DCS VUR EK–HK Controls
D
Novel genomic disorders
Population frequency (%)
Type
Deletion
Duplication
CAKUT KA OU PUV DCS VUR

Figure 2

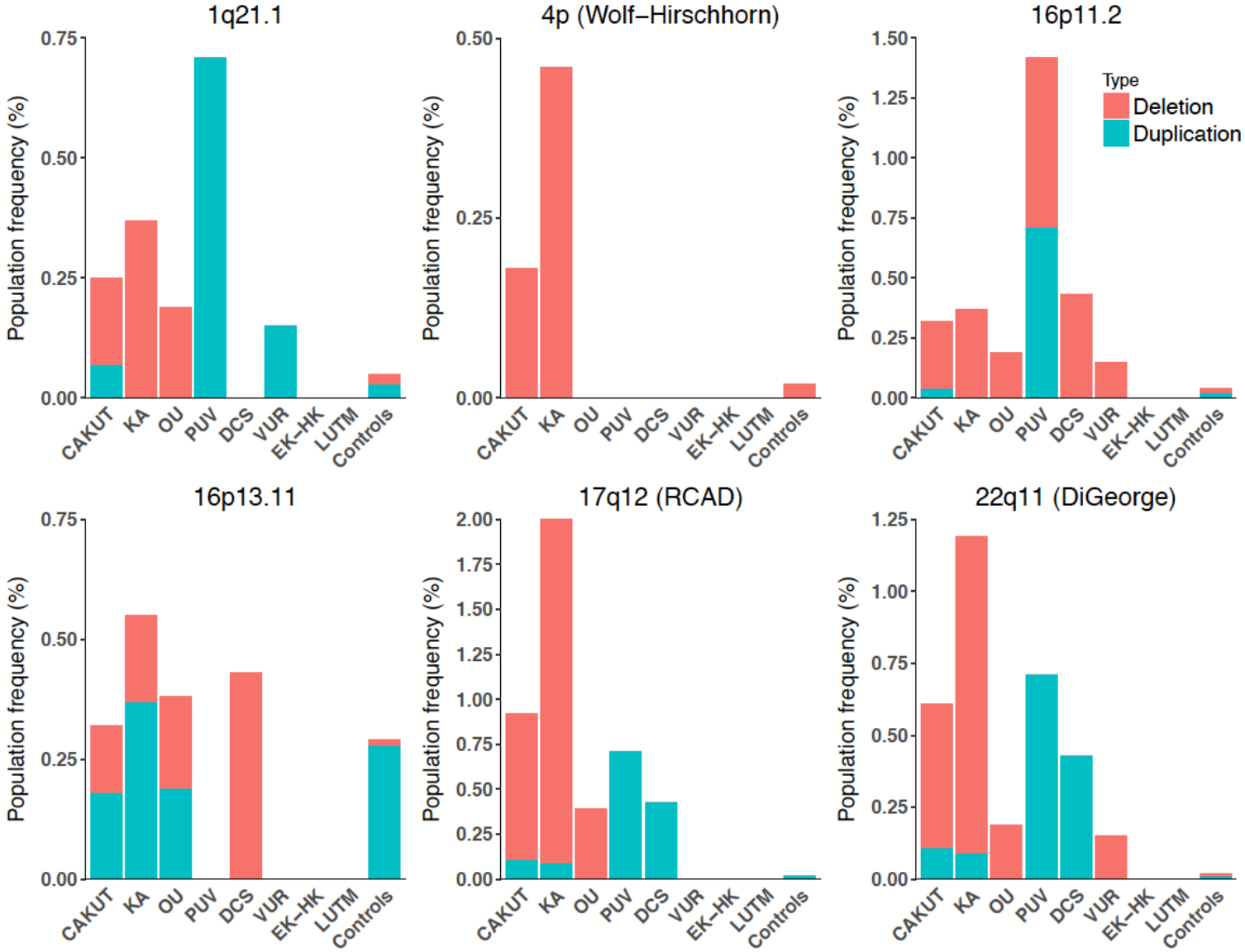

1q21.1
4p (Wolf–Hirschhorn)
16p11.2
16p13.11
17q12 (RCAD)
22q11 (DiGeorge)
Population frequency (%)
Type
Deletion
Duplication
CAKUT
KA
OU
PUV
DCS
VUR
EK–HK
LUTM
Controls

Figure 3

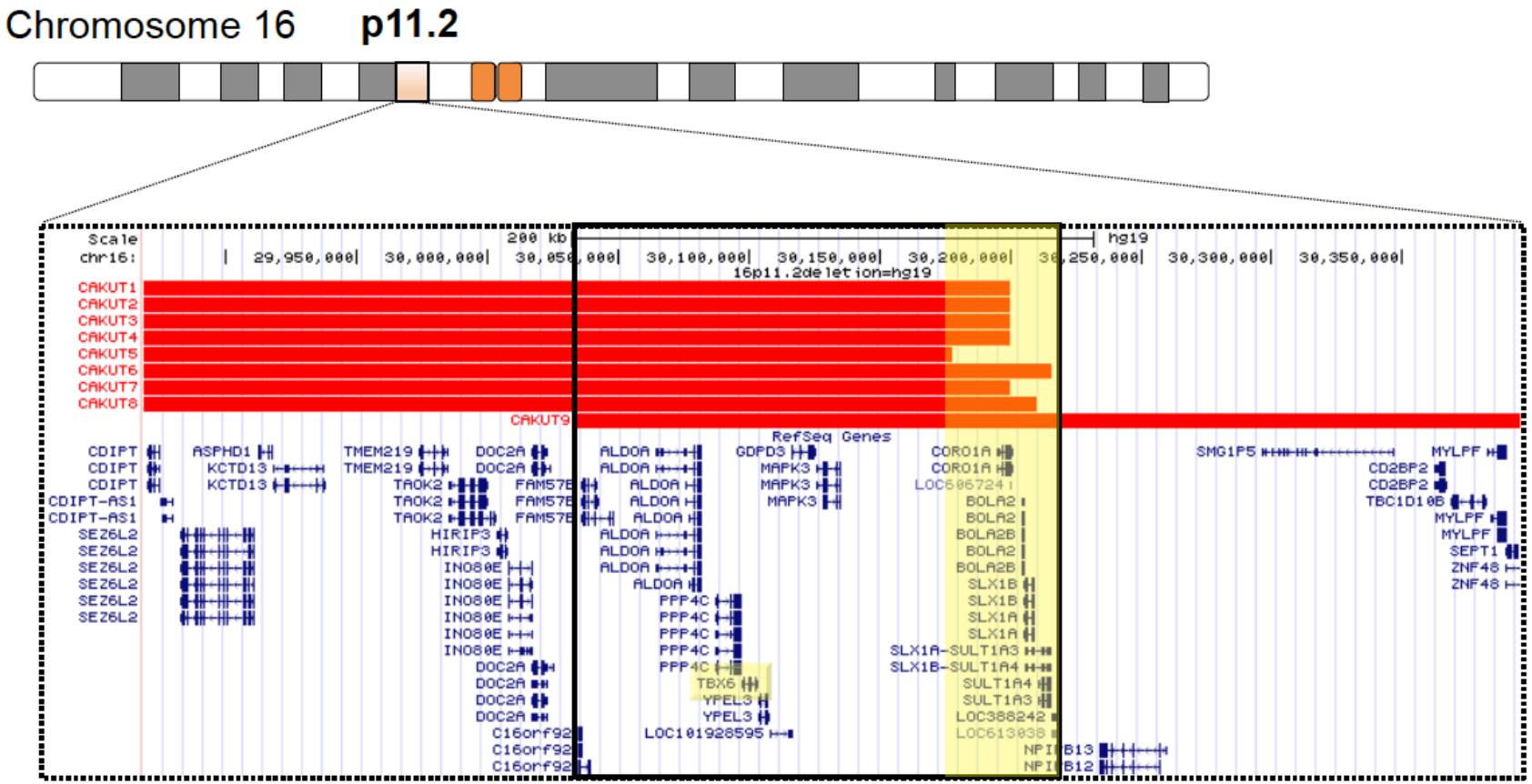

Chromosome 16
p11.2
Scale
200 kb
hg19
chr16:
29,950,000
30,000,000
30,050,000
30,100,000
30,150,000
30,200,000
30,250,000
30,300,000
30,350,000
16p11.2deletion=hg19
CAKUT1
CAKUT2
CAKUT3
CAKUT4
CAKUT5
CAKUT6
CAKUT7
CAKUT8
CAKUT9
RefSeq Genes
CDIPT
CDIPT-AS1
SEZ6L2
ASPHD1
KCTD13
TMEM219
DOC2A
TAOK2
FAM57B
HIRIP3
INO80E
C16orf92
ALDOA
GDPD3
MAPK3
PPP4C
TBX6
YPEL3
LOC101928595
CORO1A
LOC606724
BOLA2
BOLA2B
SLX1B
SLX1A
SLX1A-SULT1A3
SLX1B-SULT1A4
SULT1A4
SULT1A3
LOC388242
LOC613038
NPIP B13
NPIP B12
SMG1P5
MYLPF
CD2BP2
TBC1D10B
SEPT1
ZNF48

Figure 4

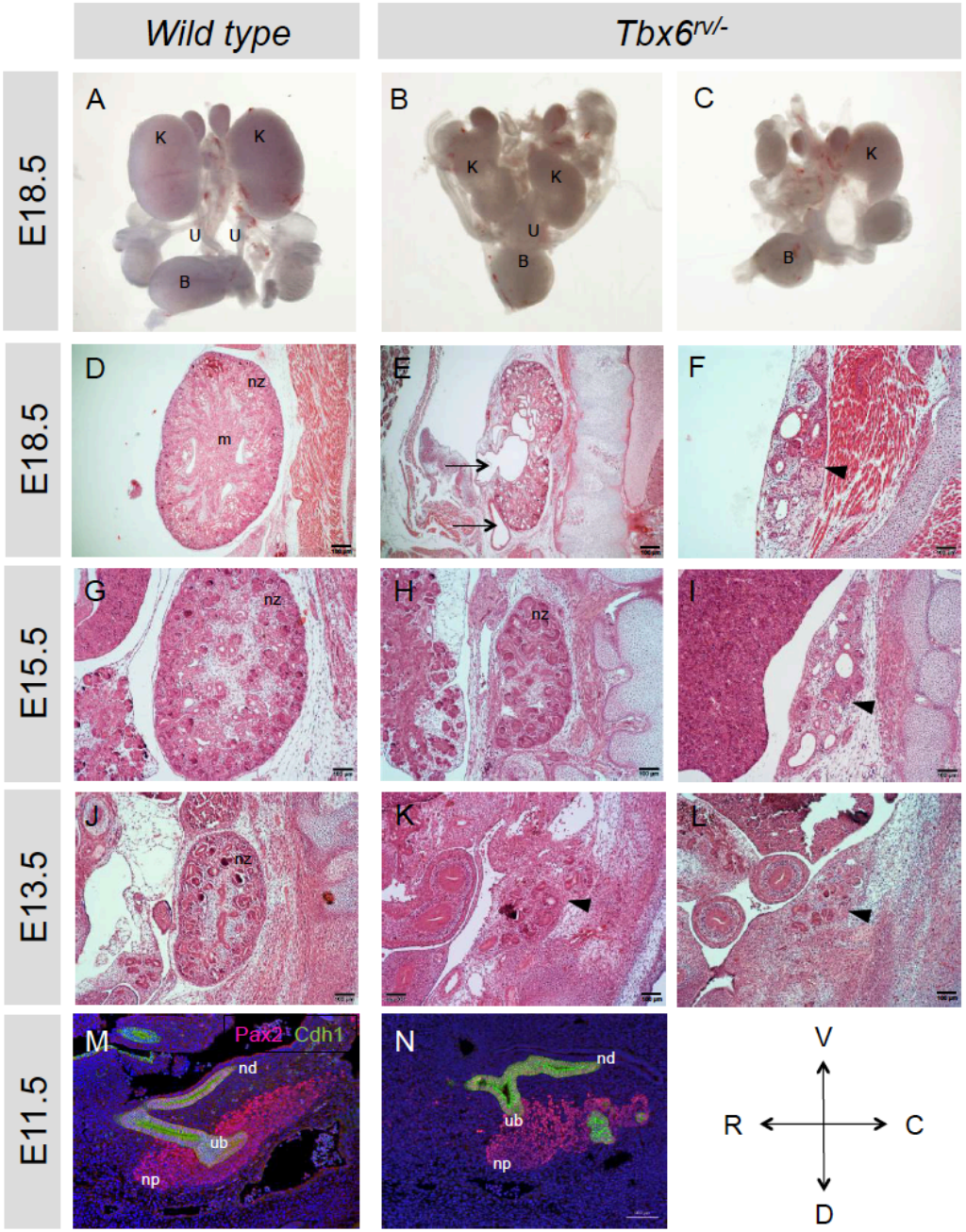
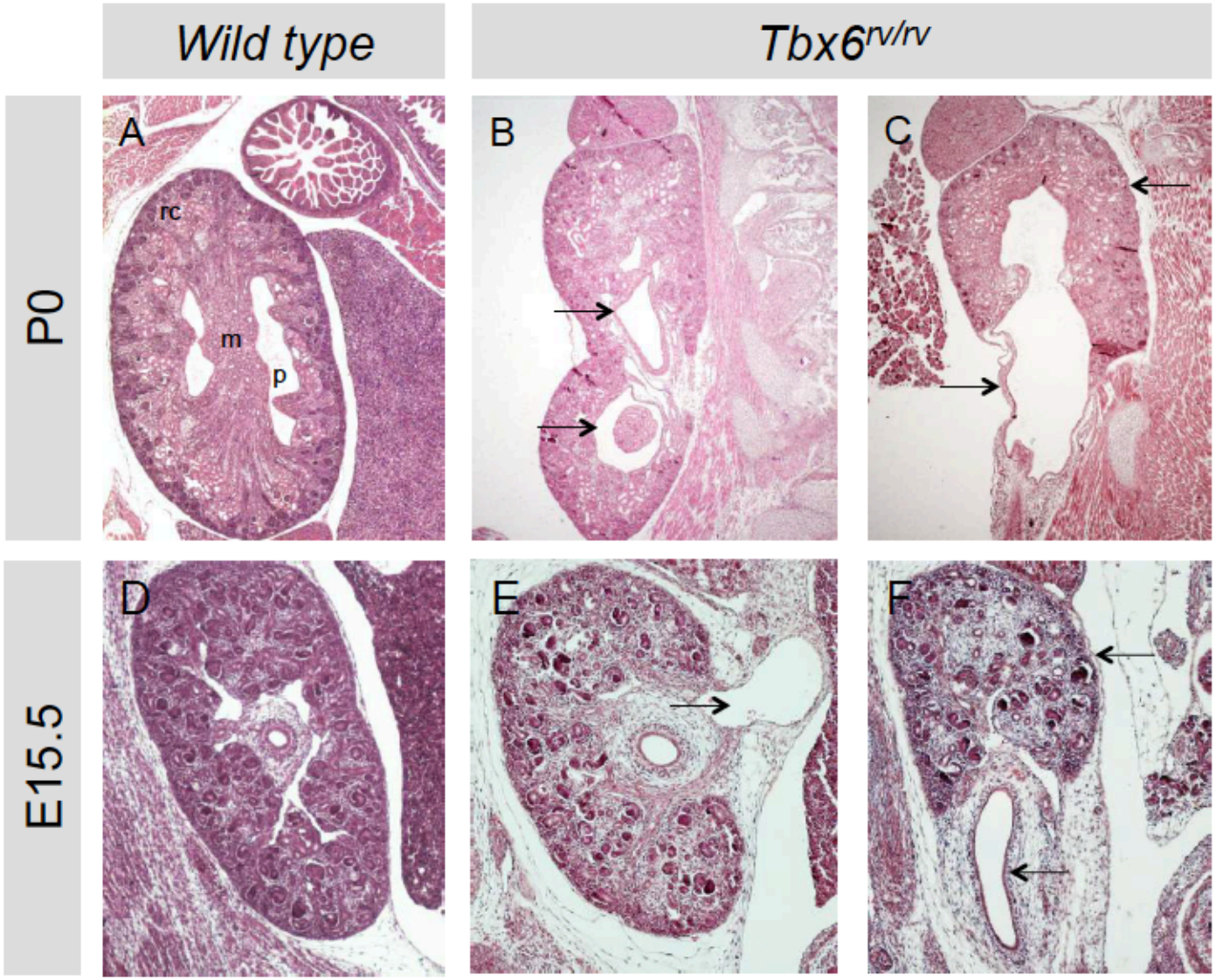

Wild type
Tbx6rv/-
E18.5
E18.5
E15.5
E13.5
E11.5
A
K
K
U
U
B
B
K
K
U
B
C
K
B
D
nz
m
E
F
G
nz
H
nz
I
J
nz
K
L
M
Pax2 Cdh1
nd
ub
np
N
nd
ub
np
V
R
C
D

Figure 5



Hindawi Publishing Corporation
Clinical and Developmental Immunology
Volume 2013, Article ID 597920, 14 pages
http://dx.doi.org/10.1155/2013/597920

Review Article

Interactions between Cytokines, Congenital Anomalies of Kidney and Urinary Tract and Chronic Kidney Disease

Ana Cristina Simões e Silva,[1,2,3] Flávia Cordeiro Valério,[1,3] Mariana Affonso Vasconcelos,[1] Débora Marques Miranda,[1,2] and Eduardo Araújo Oliveira[1,2]

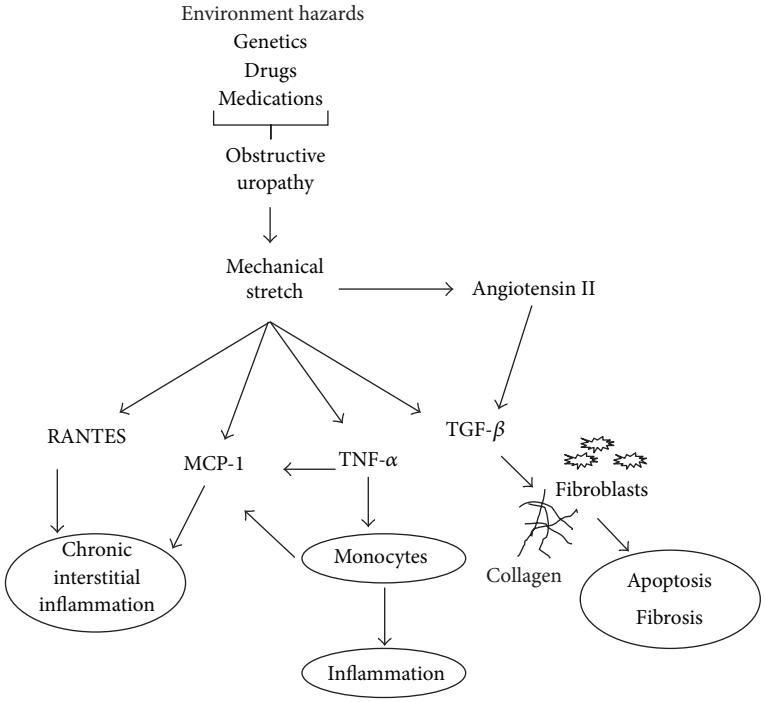


Figure 1: Potential mechanisms involved in obstructive uropathies.

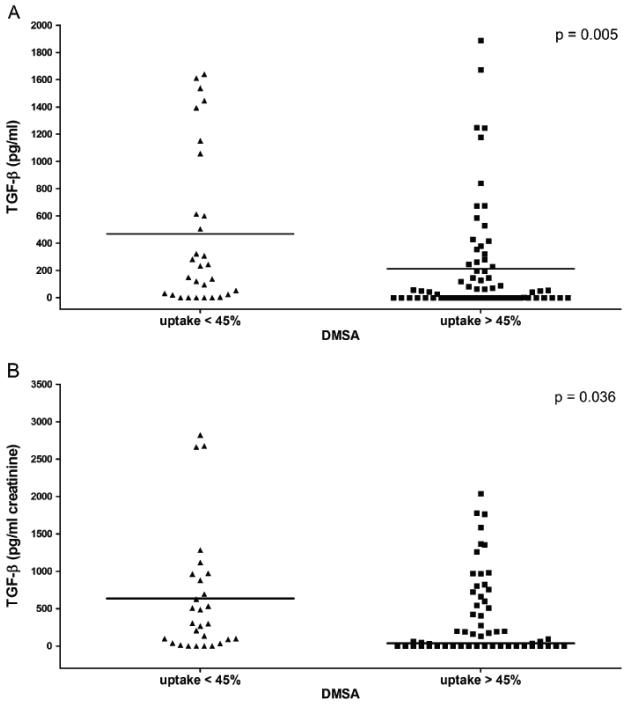
Pediatr Nephrol (2011) 26:739–747
DOI 10.1007/s00467-011-1802-4

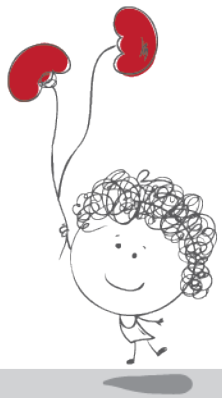
ORIGINAL ARTICLE

Urinary levels of TGF β-1 and of cytokines in patients with prenatally detected nephrouropathies

Mariana A. Vasconcelos · Maria Candida F. Bouzada · Katia D. Silveira · Leticia R. Moura · Fabiana F. Santos · Juliana M. Oliveira · Flavia F. Carvalho · Mauro M. Teixeira · Ana Cristina Simões e Silva · Eduardo A. Oliveira

Cytokines	Groups	p25	Median	p75	*p* value
TGF-β1 (pg/ml)	Idiopathic	0.000	42.00	280.00	
	Malformation	0.000	63.00	321.00	0.19
	Dysplastic	3.000	188.00	666.00	
IL-6 (pg/ml)	Idiopathic	0.000	0.0630	0.5970	
	Malformation	0.000	0.2570	0.6940	0.57
	Dysplastic	0.000	0.0695	1.0610	
TNF-α (pg/ml)	Idiopathic	0.816	1.3500	2.8890	
	Malformation	1.096	2.1150	3.2280	0.60
	Dysplastic	0.649	2.0220	3.0373	
TGF-β1/cr (pg/mg cr)	Idiopathic	0.00	62.20	758.56	
	Malformation	0.00	92.96	722.71	0.62
	Dysplastic	8.860	145.5	763.51	
IL-6/cr (pg/mg cr)	Idiopathic	0.00	0.150	3.00	
	Malformation	0.00	0.460	3.00	0.69
	Dysplastic	0.00	0.185	0.82	
TNF-α/cr (pg/mg cr)	Idiopathic	1.130	3.00	10.0	
	Malformation	0.988	2.00	7.87	0.68
	Dysplastic	0.327	2.72	5.50	





Pediatr Nephrol (2017) 32:1391–1400
DOI 10.1007/s00467-017-3614-7

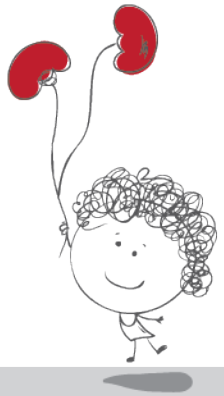
ORIGINAL ARTICLE

Posterior urethral valve in fetuses: evidence for the role of inflammatory molecules

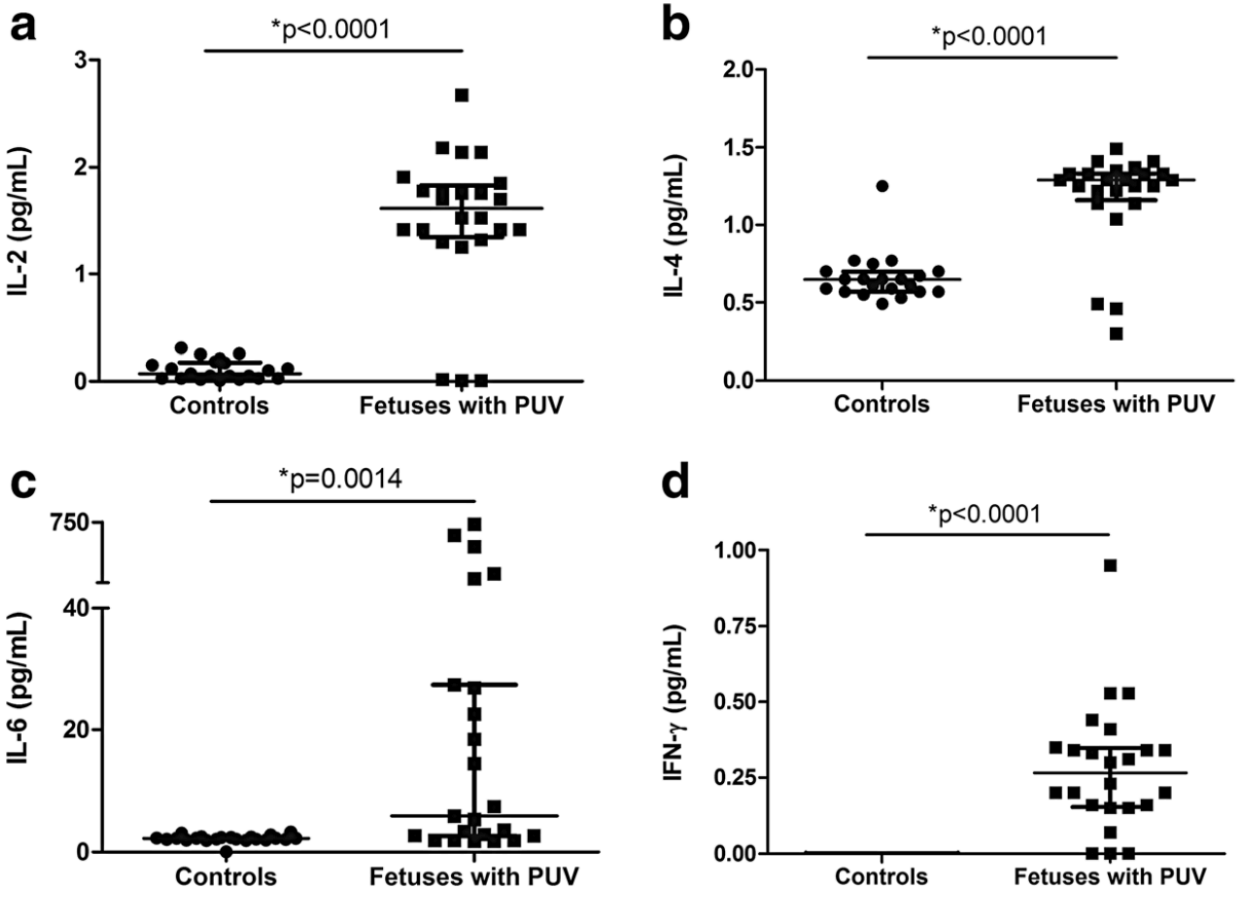
Érica Leandro Marciano Vieira[1] · Natalia Pessoa Rocha[1] · Fernando Macedo Bastos[2] · Kátia Daniela da Silveira[3] · Alamanda K. Pereira[2] · Eduardo Araújo Oliveira[2,4] · Débora Marques de Miranda[3,4] · Ana Cristina Simões e Silva[1,2,4]

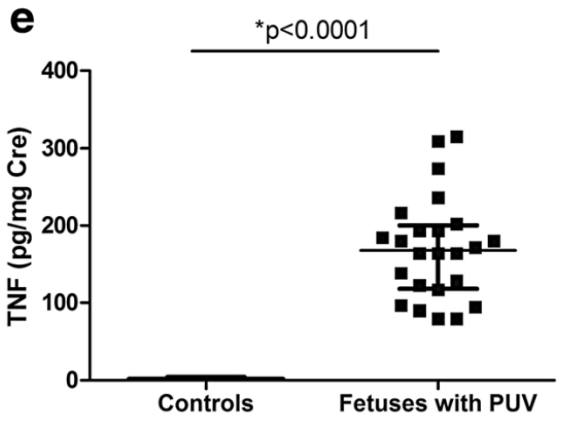
Table 1 Clinical and antenatal ultrasound findings of fetuses with posterior urethral valve

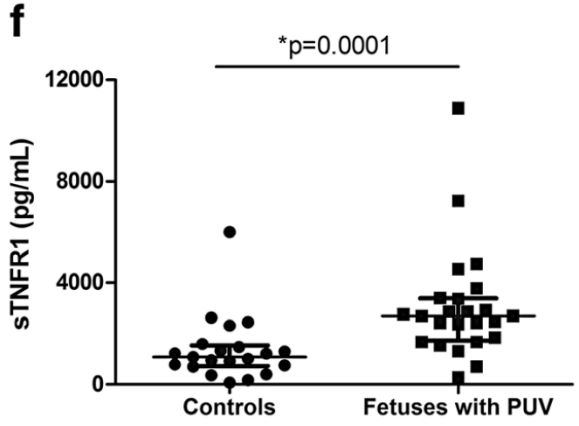
PUV patients	Findings
Gestational age (weeks)	22 ± 4
Age at birth (weeks)	36 ± 5
Echogenicity	14 (77.78%)[a]
Oligohidramnio or absence of aminiotic fluid	15 (83.33%)[a]
Hyperechogenic kidneys	14 (77.78%)[a]
Neonatal mortality	17 (70.83%)[a]

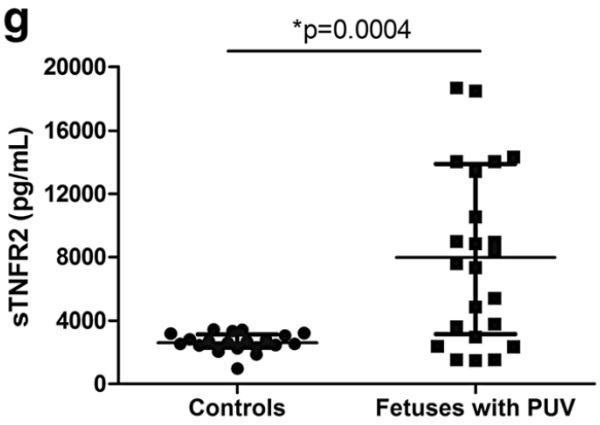


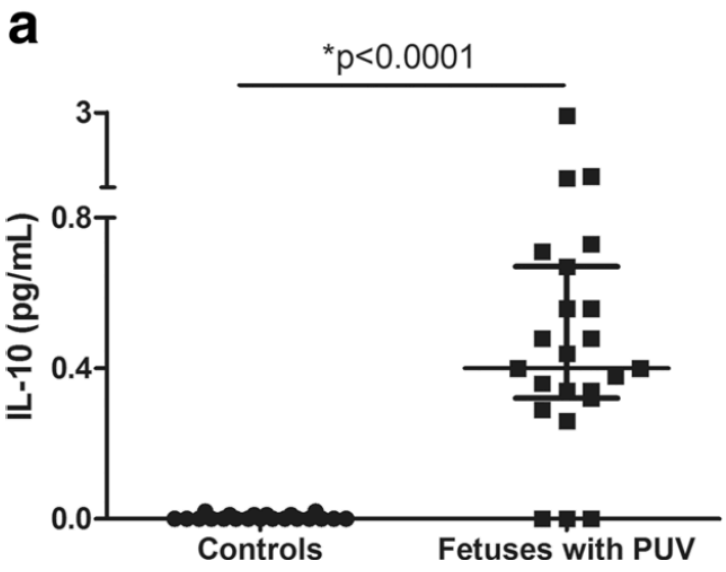
Renal function parameters	Controls	Fetuses with PUV	*p* value
Urinary osmolality (mOsm/L)	103.4 ± 3.8	161.6 ± 13.9	0.02
Urinary creatinine (mg/dL)	1.65 ± 0.05	3.48 ± 0.78	0.04
β_2-microglobulin (μg/mL)	2.04 ± 0.07	5.04 ± 0.25	0.01
Uromodulin (mg/L)	0.45 ± 0.10	2.37 ± 0.08	0.01

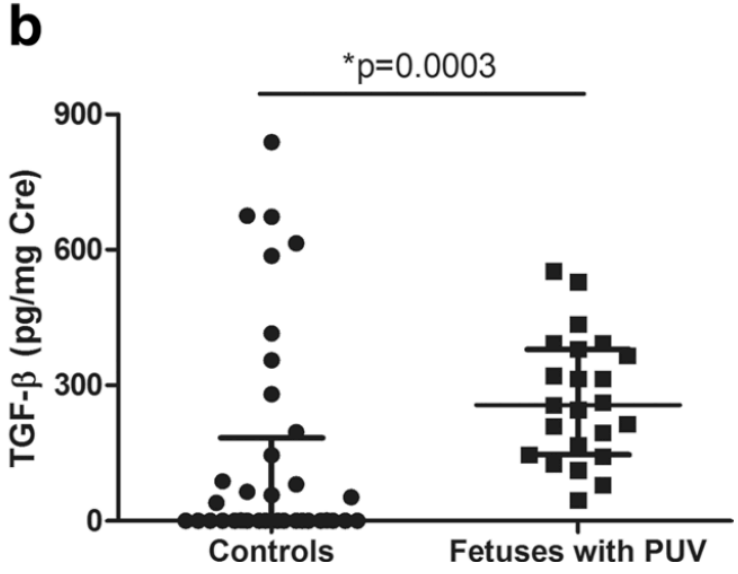


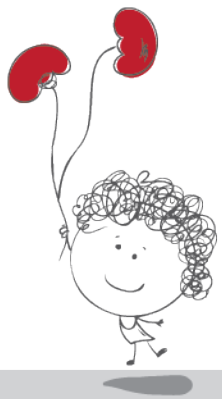

e
*p<0.0001
TNF (pg/mg Cre)
400
300
200
100
0
Controls
Fetuses with PUV

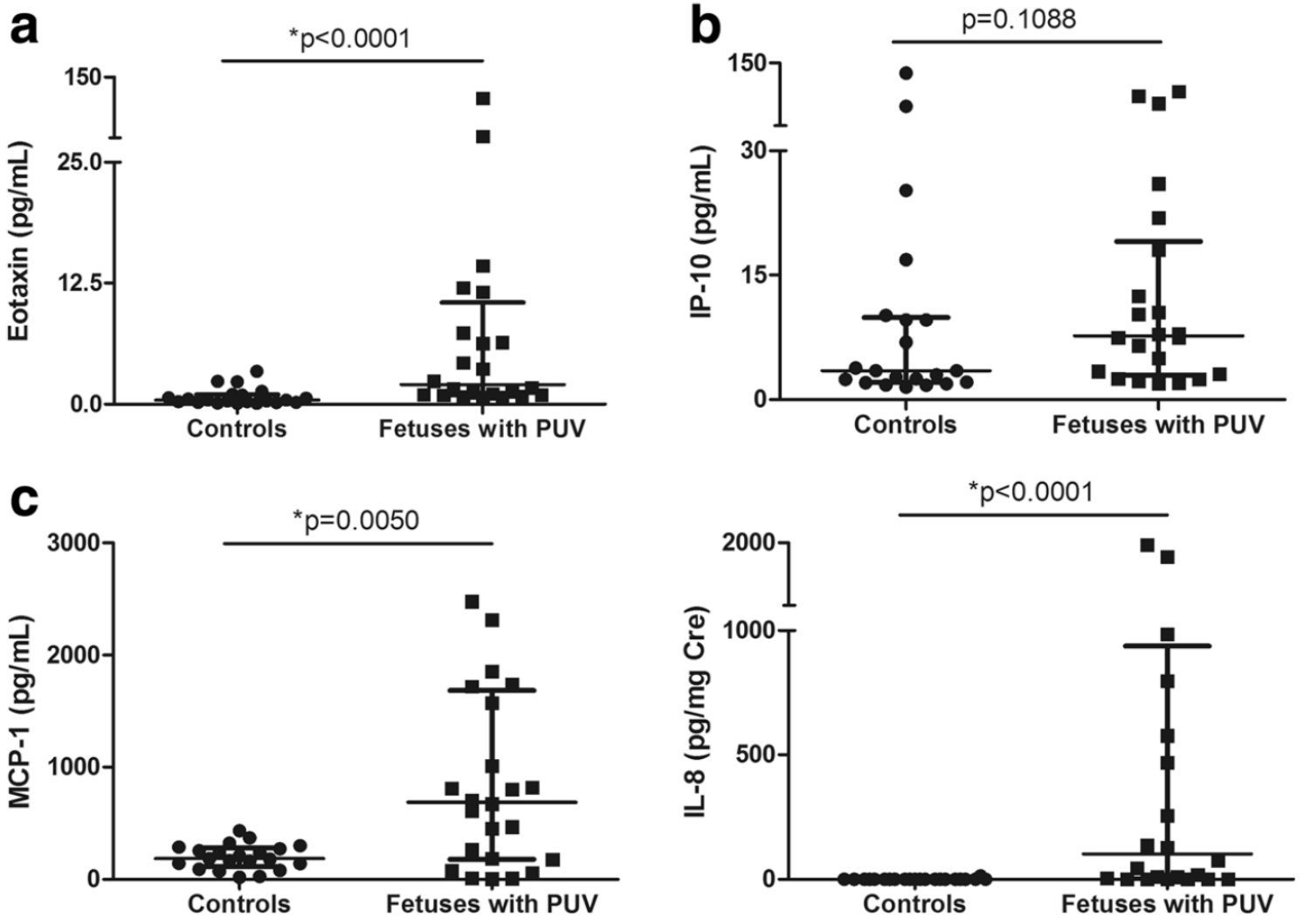

f
*p=0.0001
sTNFR1 (pg/mL)
12000
8000
4000
0
Controls
Fetuses with PUV

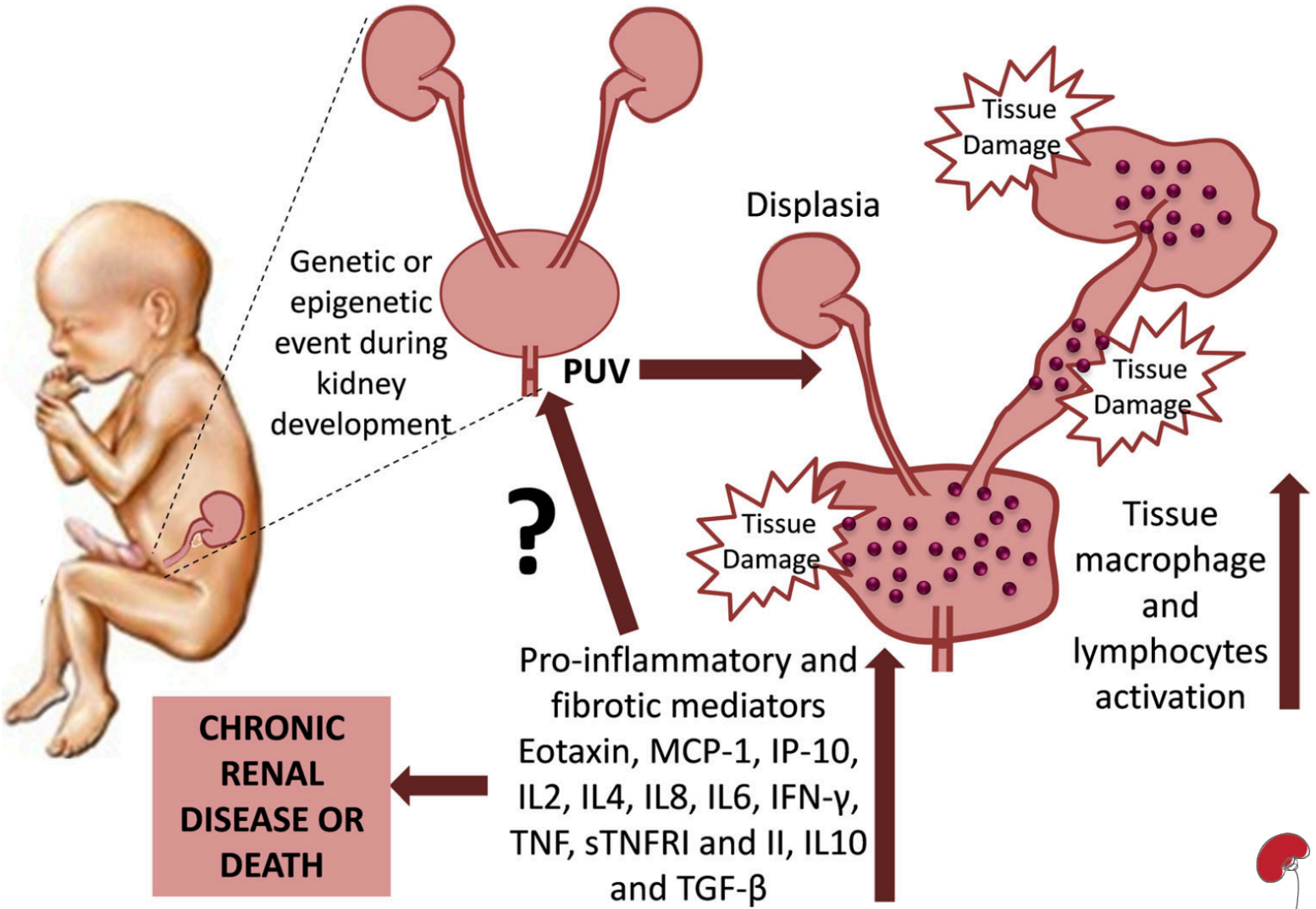

g
*p=0.0004
sTNFR2 (pg/mL)
20000
16000
12000
8000
4000
0
Controls
Fetuses with PUV


a
*p<0.0001
IL-10 (pg/mL)
3
0.8
0.4
0.0
Controls
Fetuses with PUV


b
*p=0.0003
TGF-β (pg/mg Cre)
900
600
300
0
Controls
Fetuses with PUV




a
*p<0.0001
Eotaxin (pg/mL)
150
25.0
12.5
0.0
Controls
Fetuses with PUV
b
p=0.1088
IP-10 (pg/mL)
150
30
15
0
Controls
Fetuses with PUV
c
*p=0.0050
MCP-1 (pg/mL)
3000
2000
1000
0
Controls
Fetuses with PUV
*p<0.0001
IL-8 (pg/mg Cre)
2000
1000
500
0
Controls
Fetuses with PUV


Genetic or epigenetic event during kidney development
PUV
Displasia
Tissue Damage
Tissue Damage
Tissue Damage
?
Tissue macrophage and lymphocytes activation
Pro-inflammatory and fibrotic mediators
Eotaxin, MCP-1, IP-10, IL2, IL4, IL8, IL6, IFN-γ, TNF, sTNFRI and II, IL10 and TGF-β
CHRONIC RENAL DISEASE OR DEATH

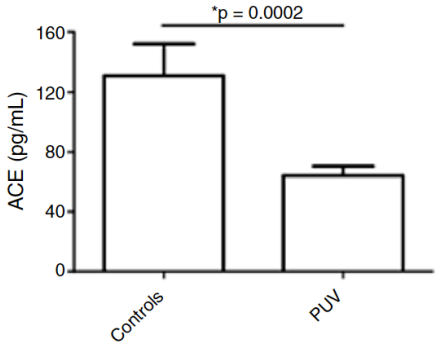
J Pediatr (Rio J). 2018;xxx(xx):xxx–xxx

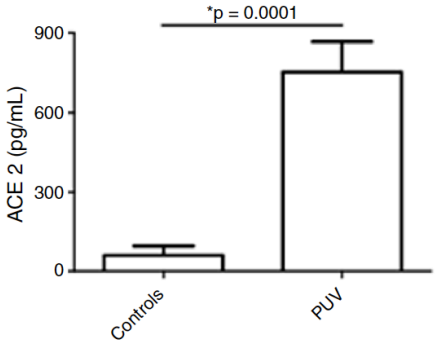
Jornal de Pediatria
www.jped.com.br

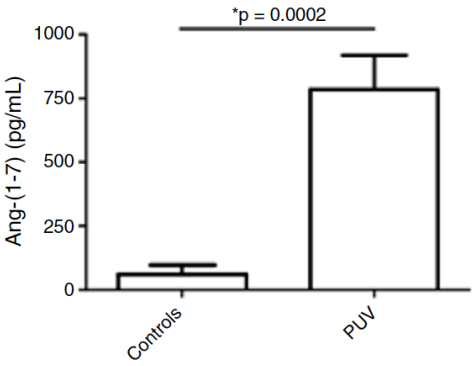
ORIGINAL ARTICLE

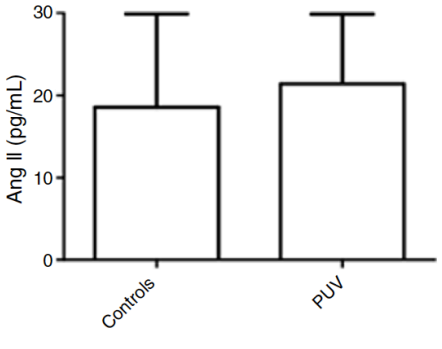
The protective arm of the renin–angiotensin system may counteract the intense inflammatory process in fetuses with posterior urethral valves☆

Natalia P. Rocha[a], Fernando M. Bastos[a,b], Érica L.M. Vieira[a], Thiago R.R. Prestes[a], Katia D. da Silveira[a], Mauro M. Teixeira[a,c], Ana Cristina Simões e Silva[a,*]









Pharmacological Research 107 (2016) 154–162

Contents lists available at ScienceDirect

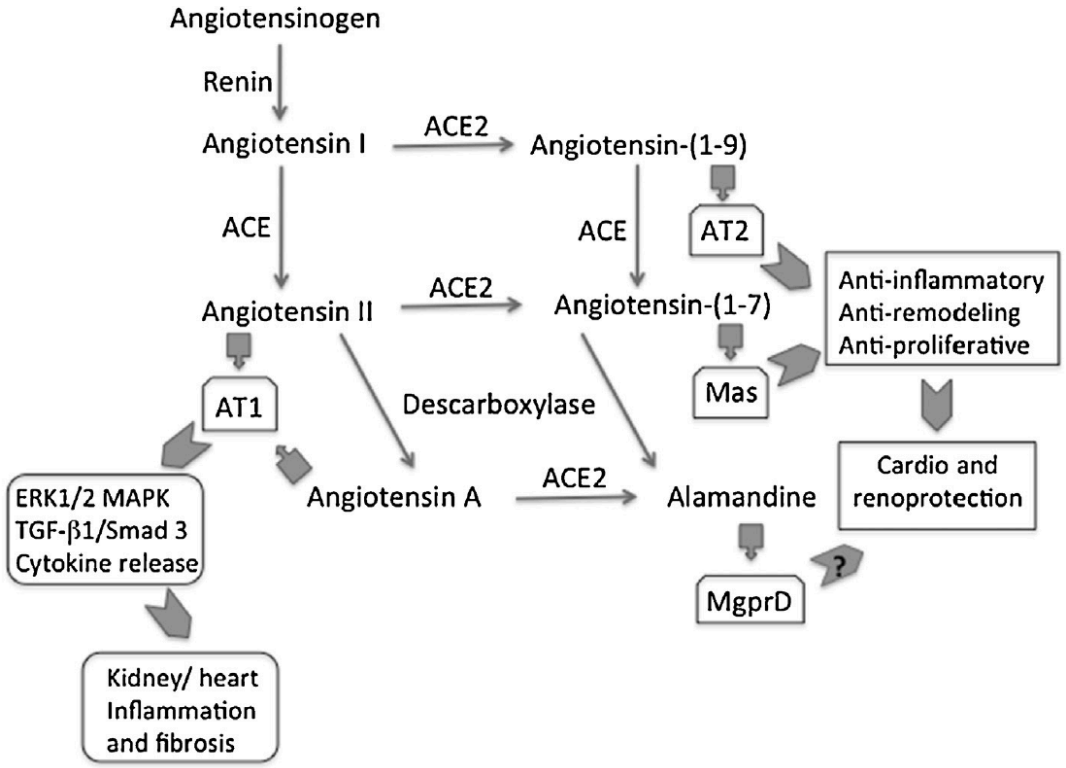
Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Perspective

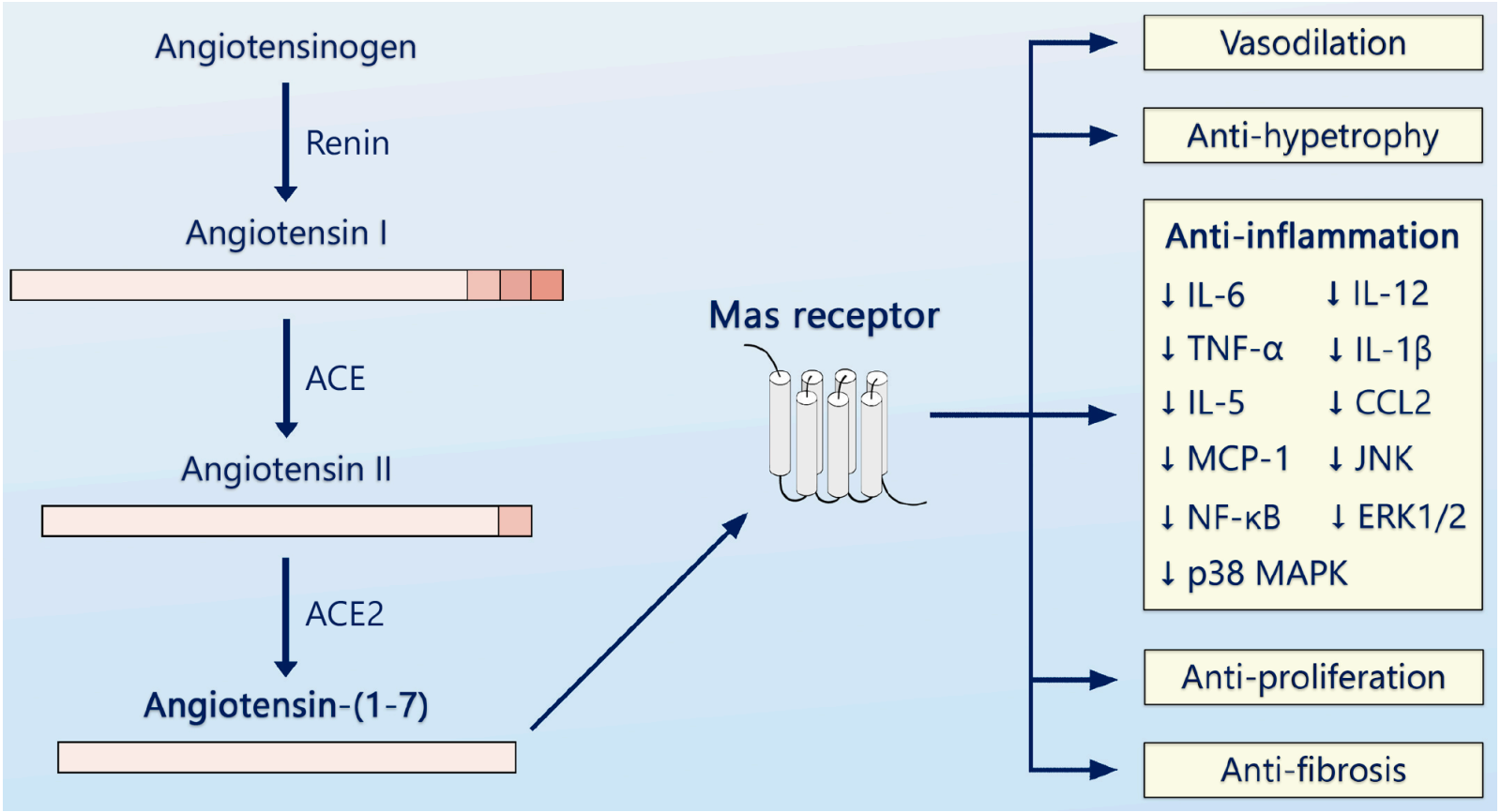
ACE inhibition, ACE2 and angiotensin-(1–7) axis in kidney and cardiac inflammation and fibrosis

Ana Cristina Simões e Silva[a,*], Mauro Martins Teixeira[b]



Doenças renais

Perspectivas terapêuticas

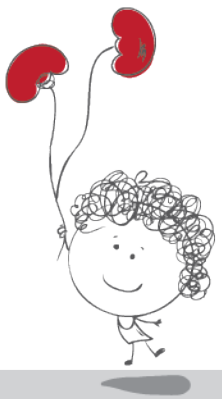


Prestes et al. Current Drug Targets 2017; 18: 1301-1303.

Malformações dos rins e do trato urinário

Polimorfismos de genes que participam da embriogênese dos rins e do trato urinário (BMP-4, PAX-2 e AGTR2) estão associados a diferentes expressões clínicas (OJUP, RVU, RDM) de CAKUT.

Anomalias renais se associam a CNVs afetando regiões codificadoras, incluindo desordens genômicas associadas às CNVs (GD-CNV) e a novas deleções. Uropatias obstrutivas tem menor CNV e prevalência intermediária de GD-CNV. O RVU possui o menor GD-CNV, mas alta prevalência de novos CNVs exônicos, particularmente duplicações. O gene TBX6 está relacionado a todo espectro de CAKUT.



Malformações dos rins e do trato urinário

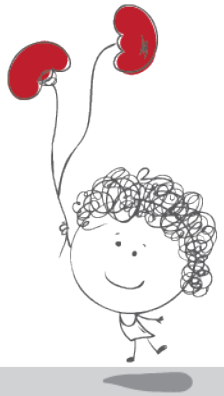
Marcadores inflamatórias, moléculas fibrogênicas e compoentes do SRA exercem importante papel na fisiopatologia das malformações dos rins e do trato urinário.

TGF-beta urinário está aumentado em crianças com rins que apresentam função comprometida à cintilografia renal estática.

Inúmeras quimiocinas e citocinas estão intensamente aumentadas na urina de fetos com válvula de uretra posterior.

ECA2 e Ang-(1-7) também estão significativamente aumentadas na urina de fetos com válvula de uretra posterior.

Há interação entre o SRA e marcadores de inflamação e fibrose em fetos com válvula de uretra posterior.



Clinical and Translational Medicine
a SpringerOpen Journal

PERSPECTIVE Open Access

Incorporating translational research with clinical research to increase effectiveness in healthcare for better health

Estela S Estape[1*], Mary Helen Mays[2], Rosanne Harrigan[3] and Robert Mayberry[4]

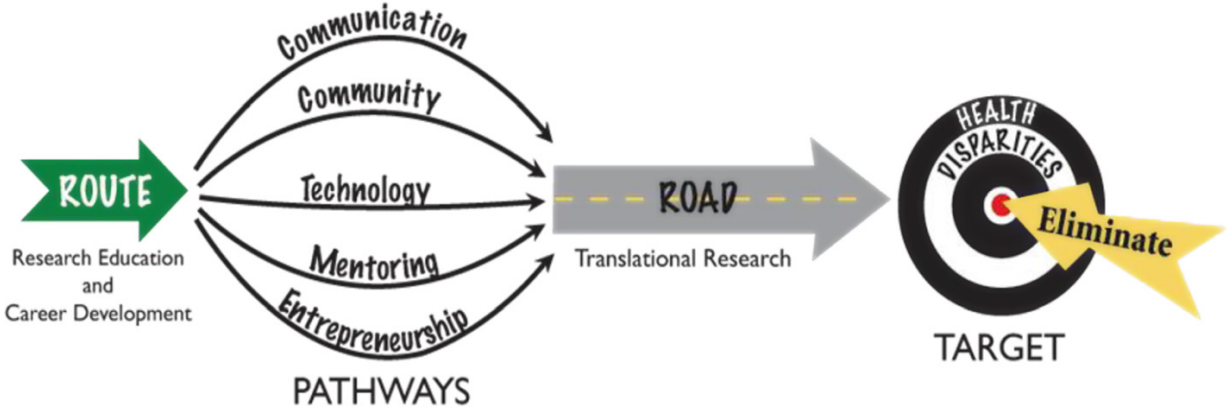
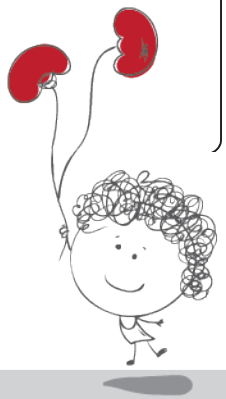


Figure 1 Translational research education pathways to eliminate health disparities.



Conflito de interesse: Nenhum

Agradecimentos

Laboratório Interdisciplinar de Investigação Médica

Fapemig

CNPq

INCT – Instituto Nacional de Ciência e Tecnologia de Medicina Molecular

CAPES