Os rins no Complexo Esclerose Tuberosa: O que precisamos saber ?

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Universidade Federal do Paraná
Complexo Hospital de Clínicas – UFPR

Conflitos de interesse

- ✔ Membro do COMDORA.
- ✔ Participação em mutirões de atendimento multidisciplinar de pacientes com complexo esclerose tuberosa.
- ✔ Aumentar o interesse e dos Nefrologistas no cuidado de pacientes com doenças renais genéticas raras, como o complexo esclerose tuberosa !

Breves informações gerais

- Descrição histórica:
  - ✔ 1862: Von Recklinghausen;
  - ✔ 1880: Bourneville;
- Doença rara, de herança autossômica dominante.
- Característica clínica: hamartomas em diversos órgãos.
- Incidência: 1/6.000 a 1/10.000 nascidos vivos.
- Não está relacionada à etnia, sexo, características populacionais;

  Mulheres: mais acometidas por linfagioleiomiomatose (LAM)
- Prevalência: ≈ 2.000.000 de pessoas convivem com a doença no mundo;

https://www.tscalliance.org/understanding-tsc/what-is-tsc/

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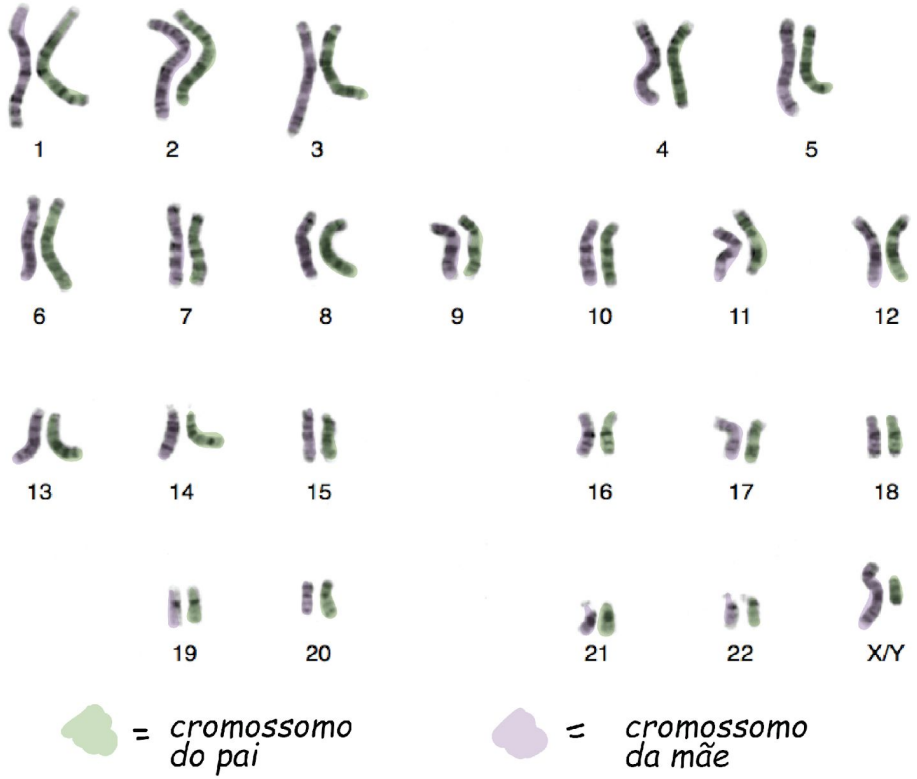
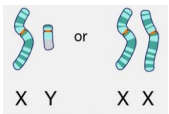
Bissler JJ, Christopher Kingswood J. Am J Med Genet Part C. 2018
Monich AG, Bissler JJ, Barreto FC. J Bras Nefrol. 2024
Lam, H.C., Siroky, B.J. & Henske, E.P. Nat Rev Nephrol, 2018.

A genética no Complexo Esclerose Tuberosa

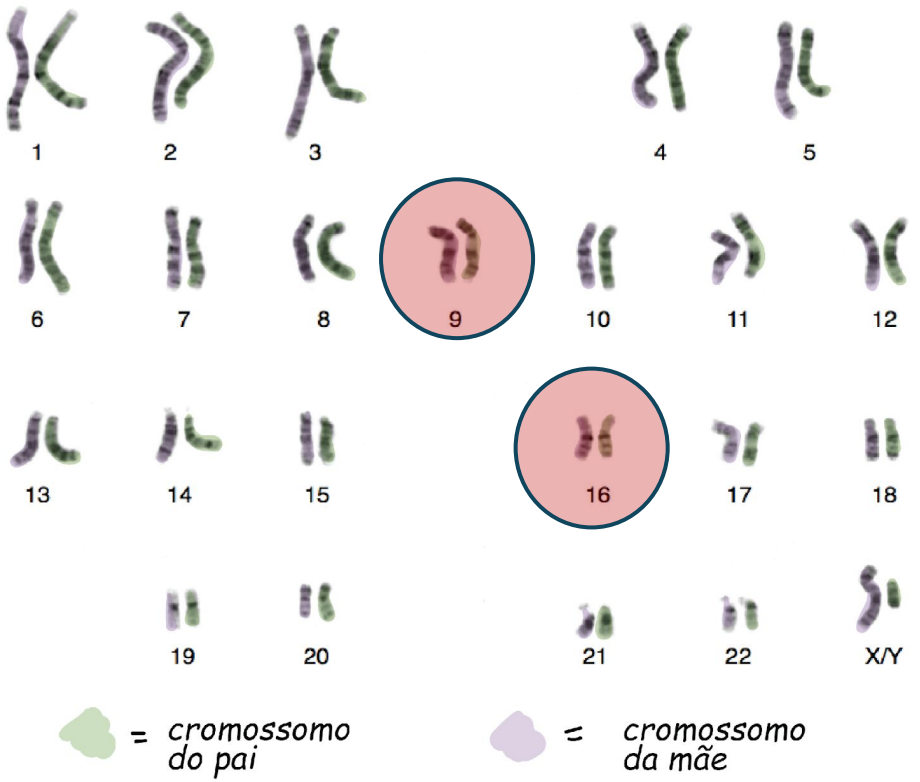


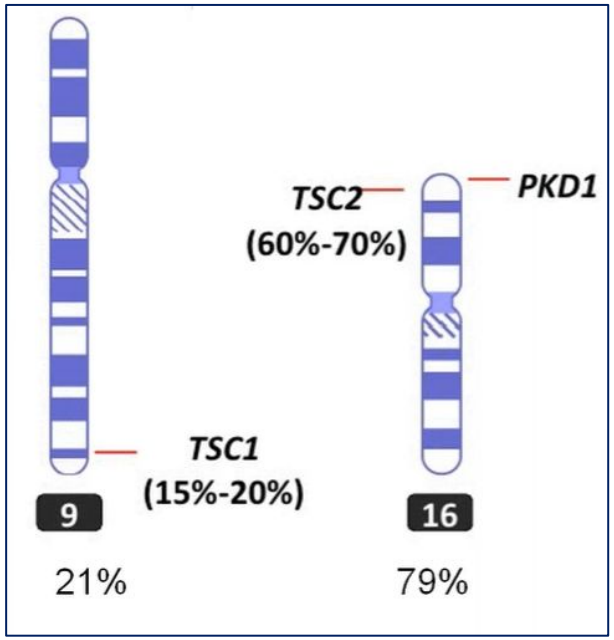
- 23 pares de cromossomos, sendo que metade é herdada da mãe, e a outra metade é herdada do pai.
- Desses 23 pares, 22 são chamados autossômicos, enquanto o outro par é o sexual.
- Sexo feminino: XX;
- Sexo masculino: XY.



https://pt.khanacademy.org/science/biology/cellular-molecular-biology/intro-to-cell-division/a/dna-and-chromosomes-article

A genética no Complexo Esclerose Tuberosa





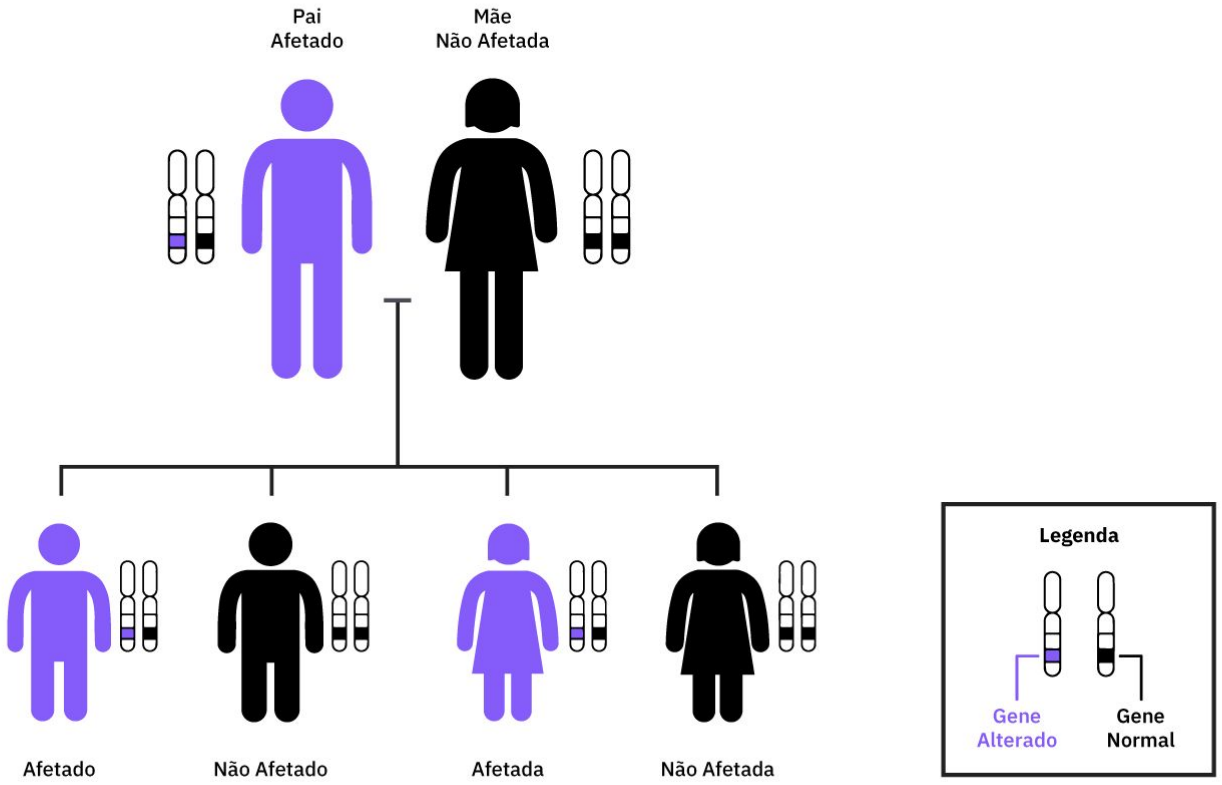
- *TSC1*: proteína hamartina.
- *TSC2*: proteína tuberina
- > 2000 variantes patogênicas.
- Variante não identificada: 10 – 15 %.
- 2/3 *de novo.*
- *TSC2* > *TSC1*

Monich AG, Bissler JJ, Barreto FC. J Bras Nefrol. 2024

https://pt.khanacademy.org/science/biology/cellular-molecular-biology/intro-to-cell-division/a/dna-and-chromosomes-article

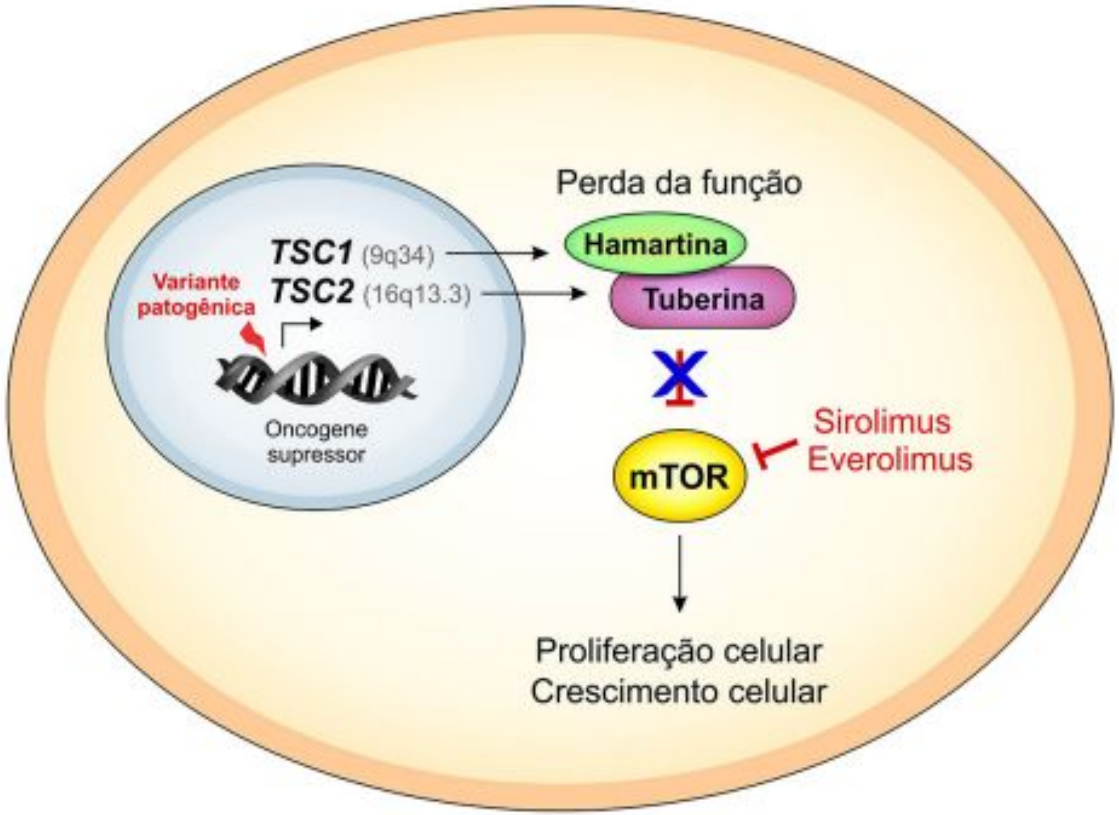
A genética no Complexo Esclerose Tuberosa

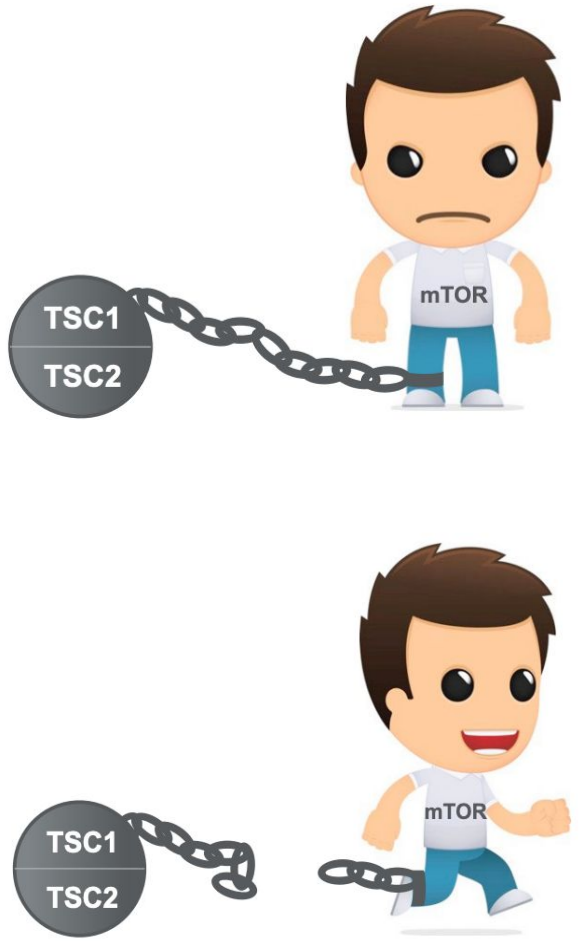
Padrão de herança
autossômica dominante



https://testedabochechinha.com.br/doenca-genetica-congenita-hereditaria/

O que acontece com as células no CET ?

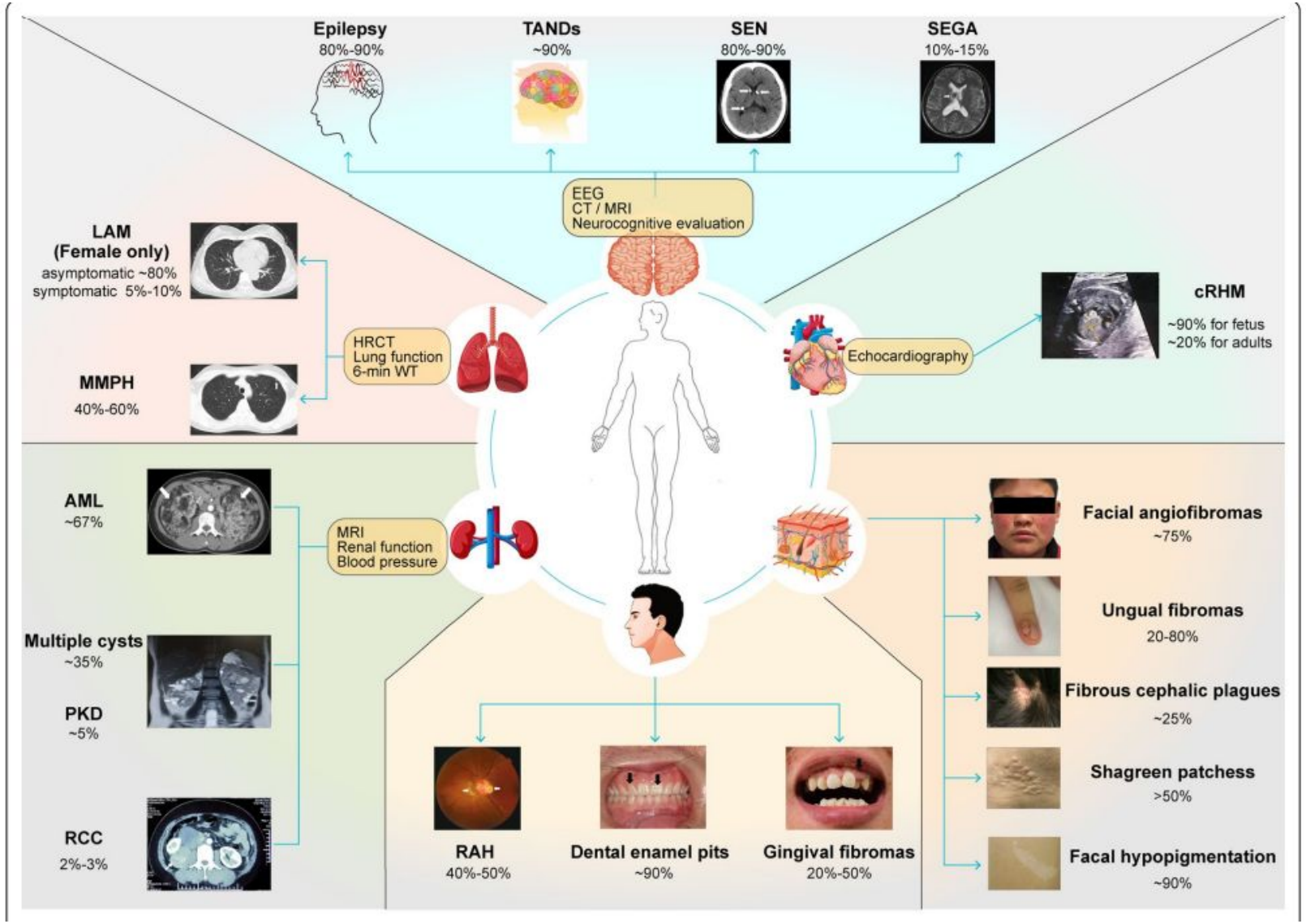




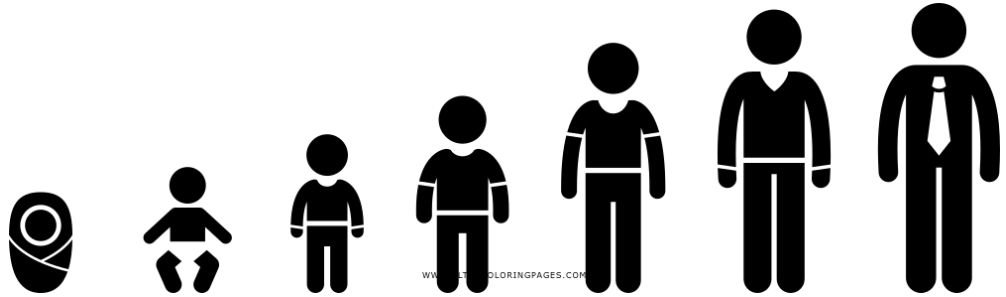
Cortesia Darcy Kruger

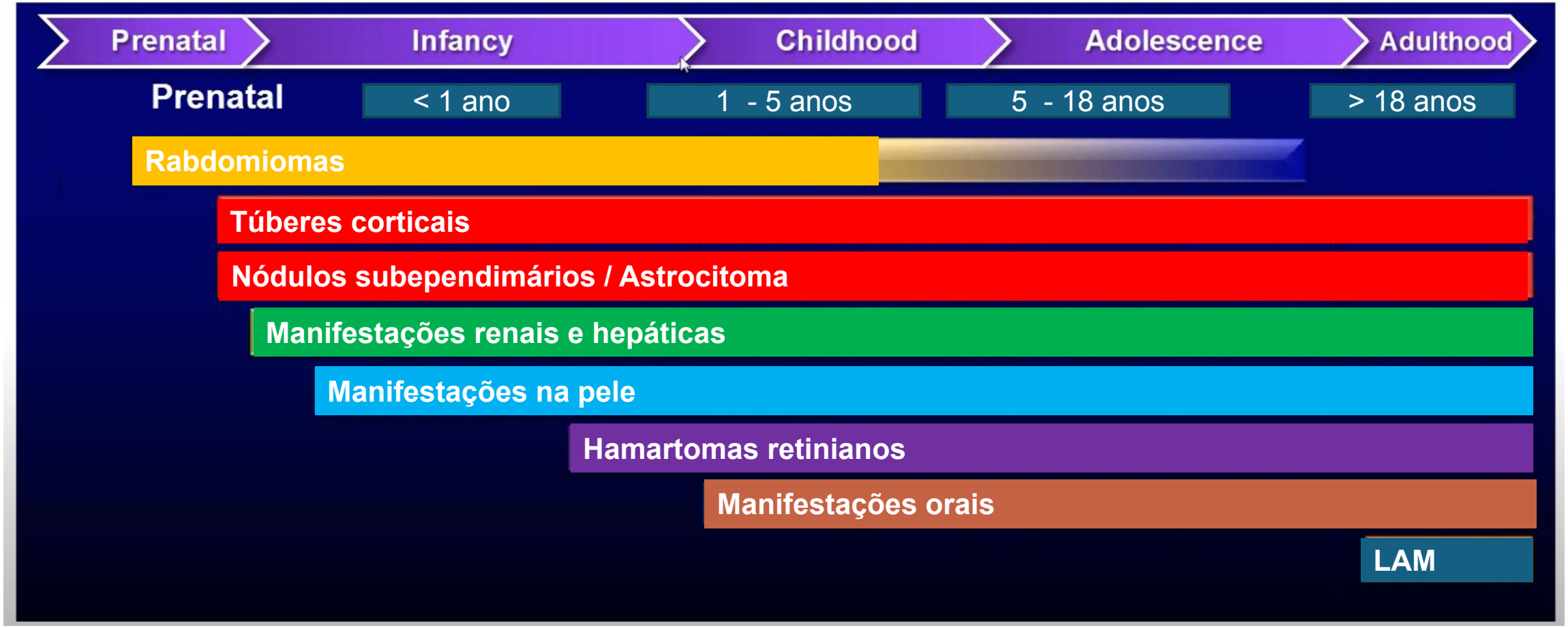
Monich AG, Bissler JJ, Barreto FC. J Bras Nefrol. 2024

DNA (gene) → proteína → célula → no corpo…



Luo, C. et al. Orphanet J Rare 2022





Curatolo, Paolo et al. The Lancet, 2008.

Critérios diagnósticos

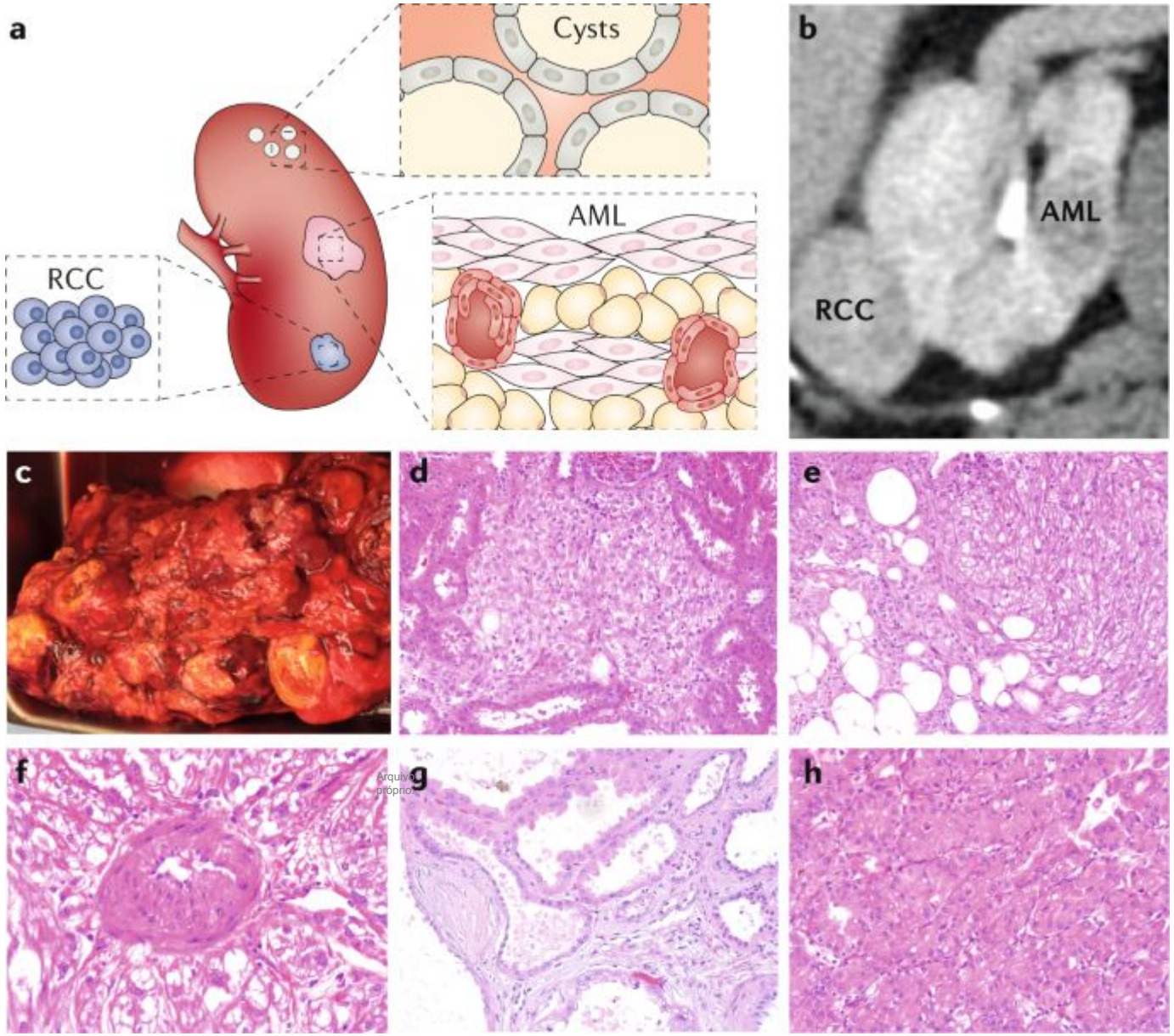
Critérios genéticos* Presença de uma variante patogênica no *TSC1* ou *TSC2*	
Critérios clínicos Necessário dois critérios maiores ou um critério maior e dois critérios menores	
Critérios maiores	Critérios menores
Angiofibromas (≥ 3) ou placa cefálica fibrosa	Corrosão do esmalte dentário (≥ 3)
Fibromas ungueais (≥ 2)	Fibromas intraorais (≥ 2)
Máculas hipomelanóticas (≥ 3, com pelo menos 5 mm de diâmetro)	Hamartoma não renal
Mancha de Shagreen	Mancha acrômica na retina
Múltiplos hamartomas na retina	Múltiplos cistos renais
Múltiplos tubérculos corticais e/ou linhas de migração radial	Lesões cutâneas do tipo "confete"
Nódulos subependimários (≥ 2)	Lesões ósseas escleróticas
Astrocitomas de células gigantes subependimais	
Angiomiolipomas renais (≥ 2)**	
Rabdomioma cardíaco	
Linfangioleiomiomatose**	

**Identificação de uma mutação genética claramente patogênica que impede a síntese proteica e/ou inativa a função das proteínas TSC1 ou TSC2; outras variantes devem ser avaliadas com cautela.*

***A combinação de angiomiolipomas e linfagioleiomiomatose sem outros achados não preenche os critérios diagnósticos.*

Monich AG, Bissler JJ, Barreto FC. J Bras Nefrol. 2024

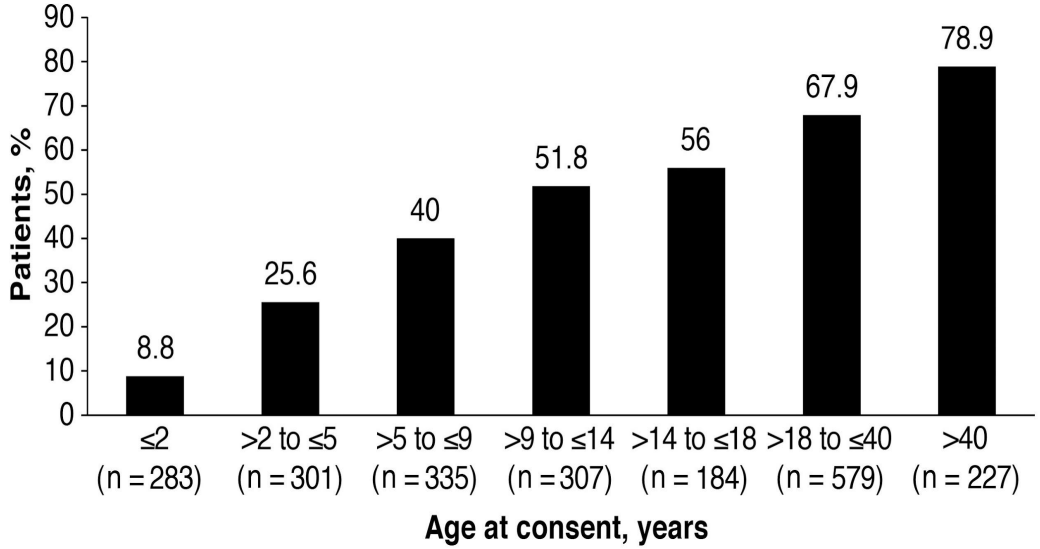
Manifestações renais & Complexo Esclerose Tuberosa

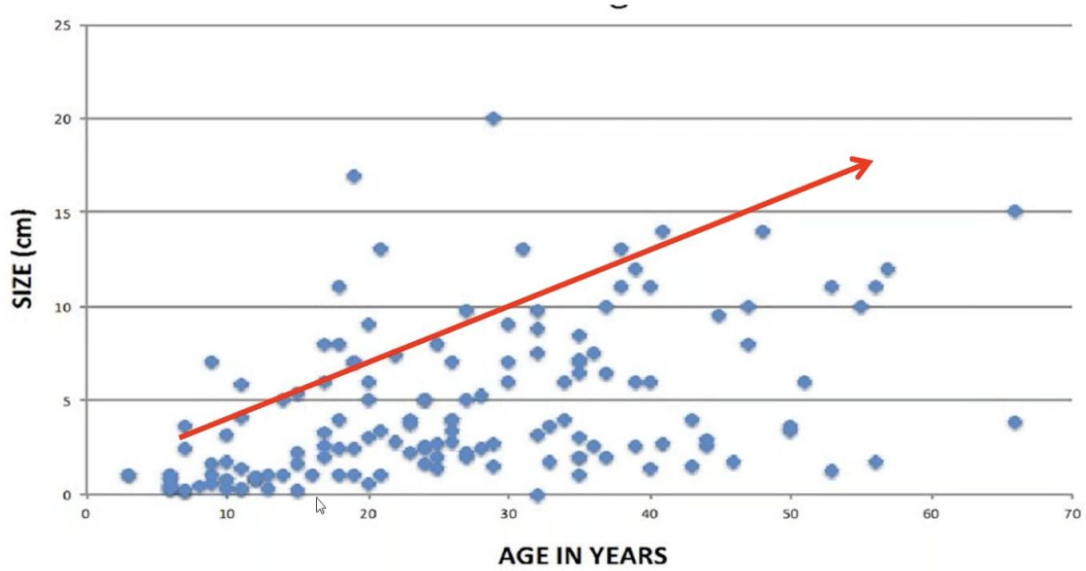


Lam, H.C., Siroky, B.J. & Henske, E.P. Nat Rev Nephrol, 2018.

Angiomiolipomas renais

- Presentes em mais da metade dos pacientes com CET.
  - até 85% dos pacientes com lesões renais.
  - População geral: 1 a 2% dos tumores renais
- Início pode ser precoce.
  - até 20% das crianças < de 2 anos de idade.
  - diagnóstico em média aos 8 anos de idade.
- Características:
  - Múltiplos, bilaterais;
  - Córtex renal;
  - Crescimento ao longo do tempo.
- Manifestações:
  - dor lombar, hematúria, massa palpável;
  - Hemorragia intratumoral ou retroperitoneal espontâneas.





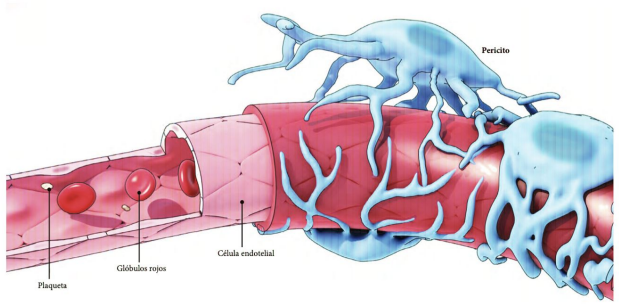
Kingswood JC et al. Nephrol Dial Transplant. 2019
Bissler JJ, Christopher Kingswood J. Am J Med Genet Part C. 2018
Lam, H.C., Siroky, B.J. & Henske, E.P. Nat Rev Nephrol, 2018.

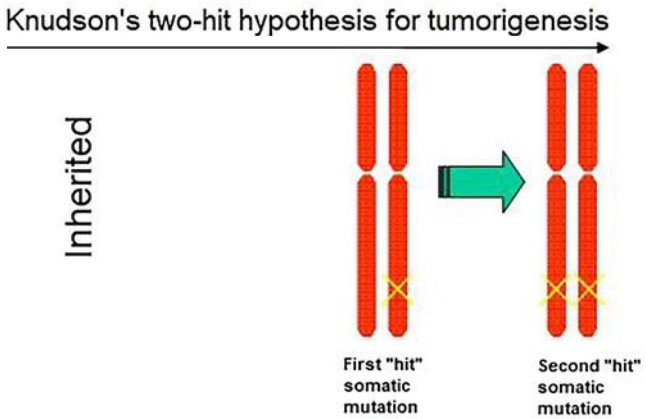
Angiomiolipomas renais

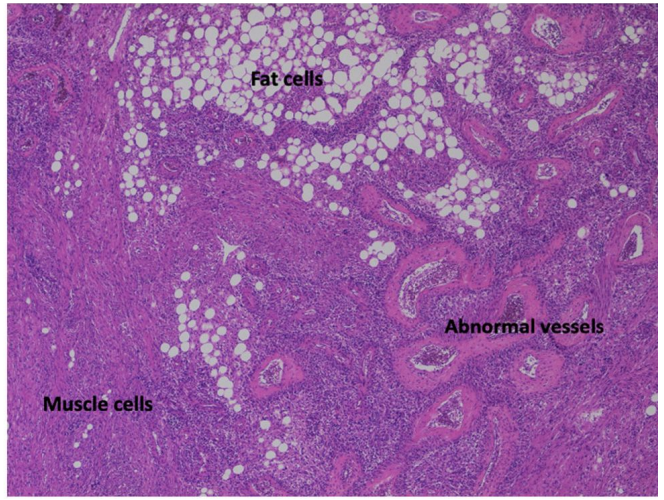
- Característica histológica:
  - ✔ Componentes vascular, adiposo e muscular liso;

- As três linhagens celulares derivam de uma célula precursora comum que sofreu inativação de ambos os alelos.
  - ✔ Segundo golpe.
  - ✔ Pericitos renais.

 Ricos ou pobres em gordura.

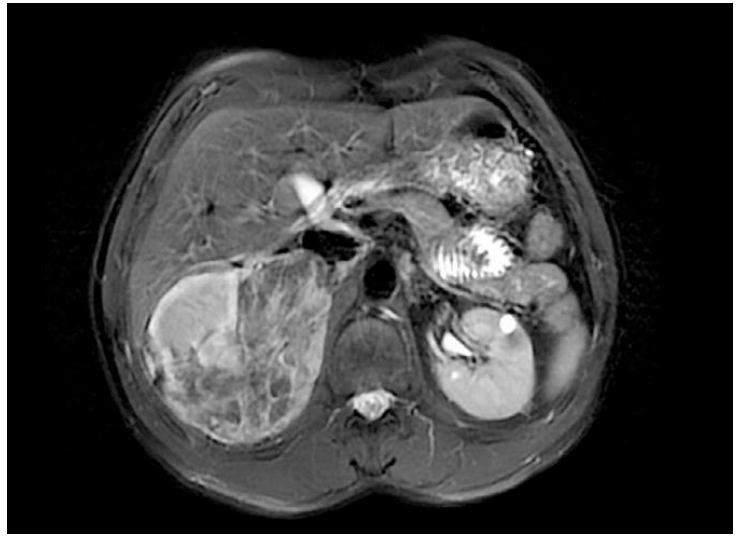


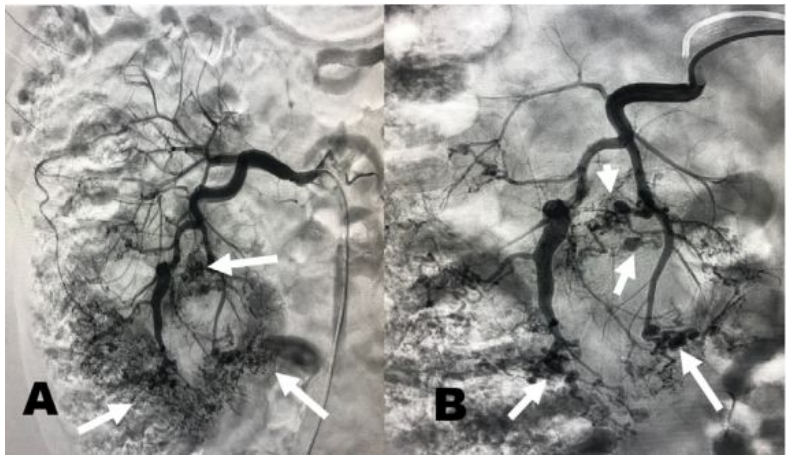


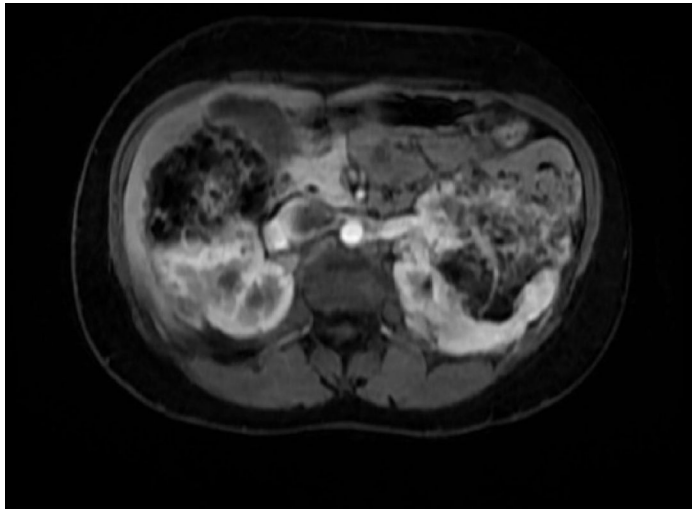


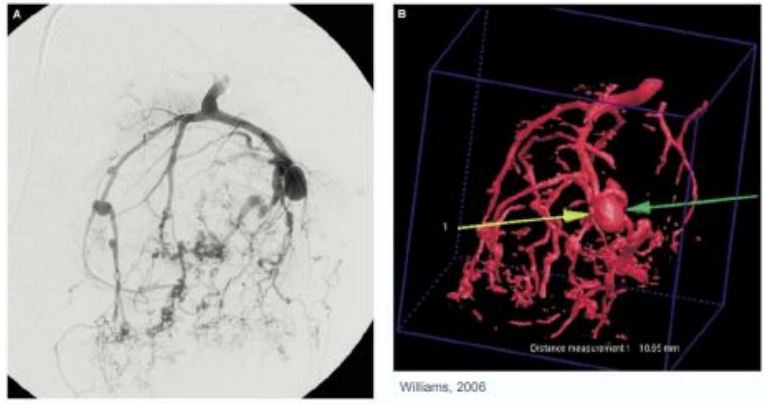
Bissler JJ, Christopher Kingswood J. Am J Med Genet Part C. 2018
Monich AG, Bissler JJ, Barreto FC. J Bras Nefrol. 2024
Lam, H.C., Siroky, B.J. & Henske, E.P. Nat Rev Nephrol, 2018.

Angiomiolipomas renais





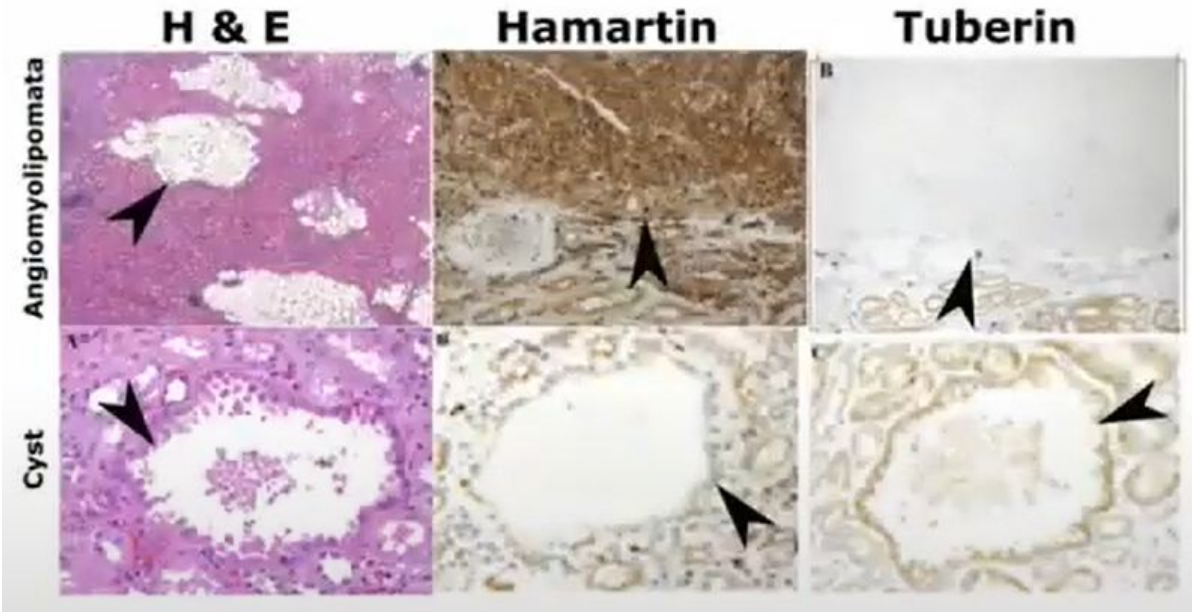




Leite T. et al. Braz. J. Nephrol. (J. Bras. Nefrol.) 2023;
Monich AG, Bissler JJ, Barreto FC. J Bras Nefrol. 2024

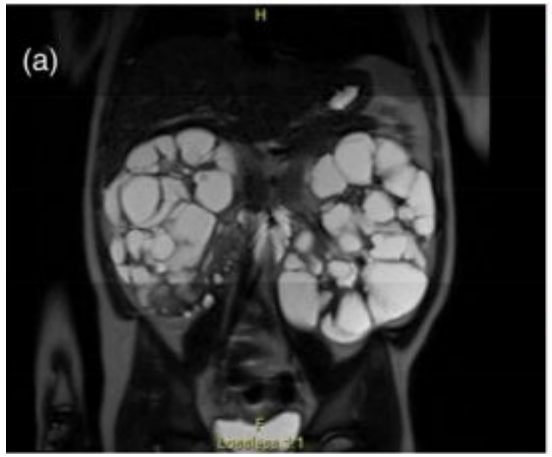
Cistos renais

- Presentes em 35 a 50% dos pacientes com CET;
- Mais frequentes TSC2.
- Significado clínico e terapêutica ?
- Mecanismo de formação diferente dos angiomiolipopmas:
    i. Haploinsuficiência é suficiente para levar a formação de cistos ?
    ii. Recrutamento de tecido / célula normal para o fenótipo modificado (doente): comunicação intercellular através de vesículas extracelulares.

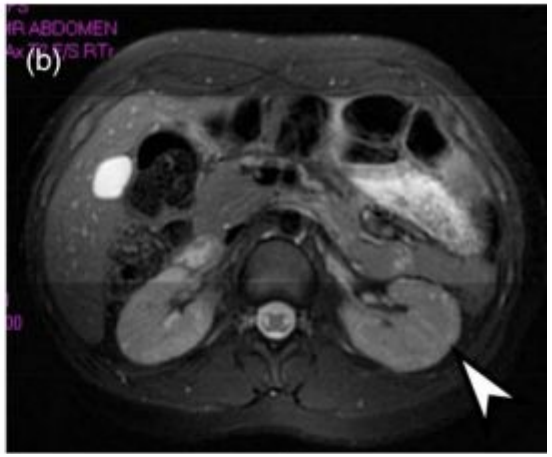


Bissler JJ, Christopher Kingswood J. Am J Med Genet Part C. 2018
Kumar P, et al. Experimental Biology and Medicine. 2021;

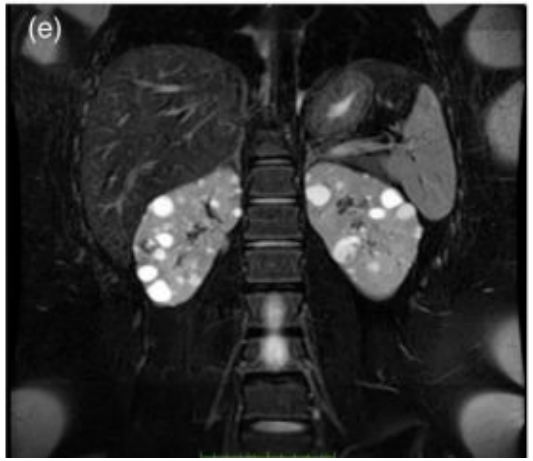
Nem todos os cistos renais são iguais….



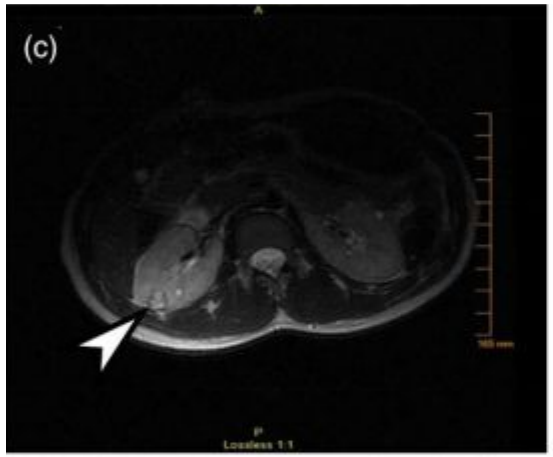
Doença policística



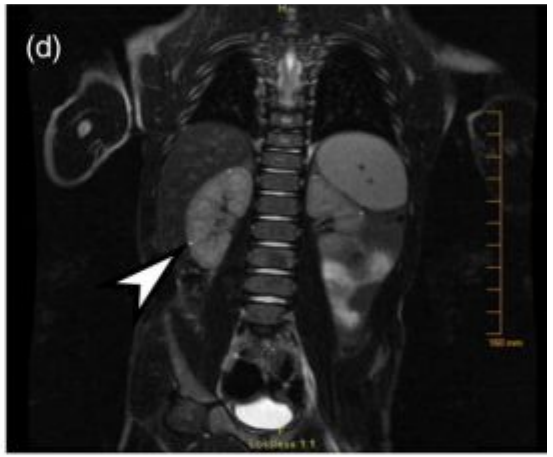
Doença microcística



Doença multicística



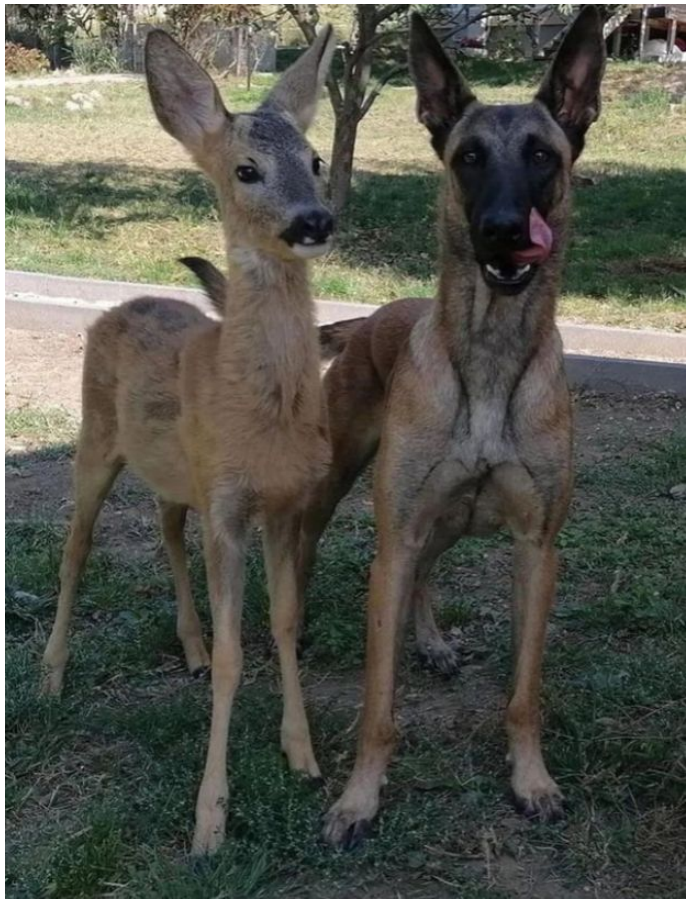
Doença cística focal



Doença cística cortical

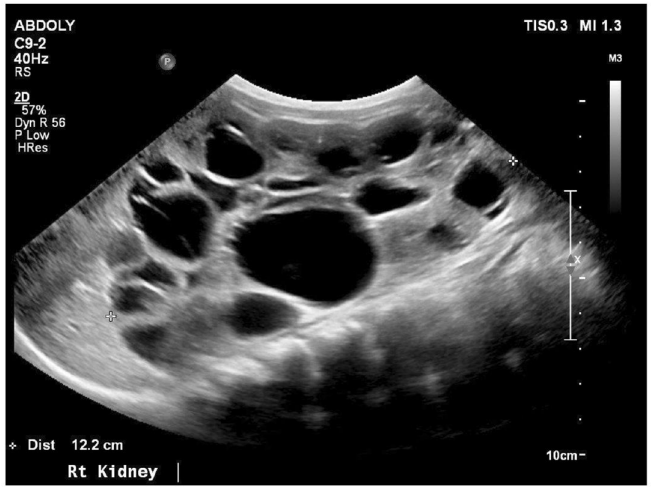
Bissler JJ, Christopher Kingswood J. Am J Med Genet Part C. 2018

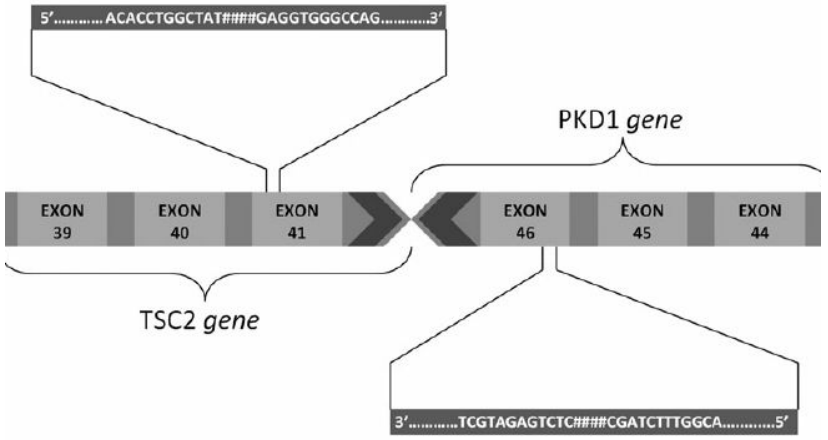
Nem todos as lesões renais são iguais….



Síndrome de deleção contígua *PKD1/TSC2*

- Síndrome de deleção contígua *PKD1/TSC2*:
  - 2 a 3% dos pacientes;
  - Grandes deleções de TSC2;
  - Doença cística grave e acelerada;
  - Múltiplos cistos presentes ao nascimento;
  - Evolução para DRC na adolescência.





Bissler JJ, Christopher Kingswood J. Am J Med Genet Part C. 2018

Nem todos os tumores renais são angiomiolipomas !

- Carcinoma células renais:
  - Risco estimado 1 a 3%;
  - Idade mais precoce (~30 anos) e mais frequente em mulheres.
  - Diagnóstico diferencial difícil com AML pobre em gordura.
    - RNM por radiologista experiente.
    - biópsia renal.

- Oncocitoma:
  - Tumor benigno raro de crescimento acelerado.
  - Solitários e unilaterais.

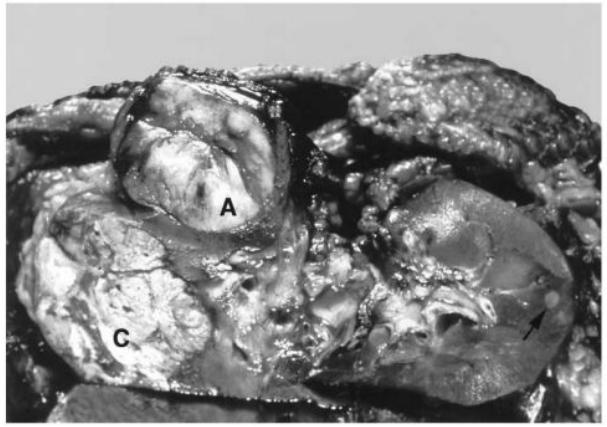
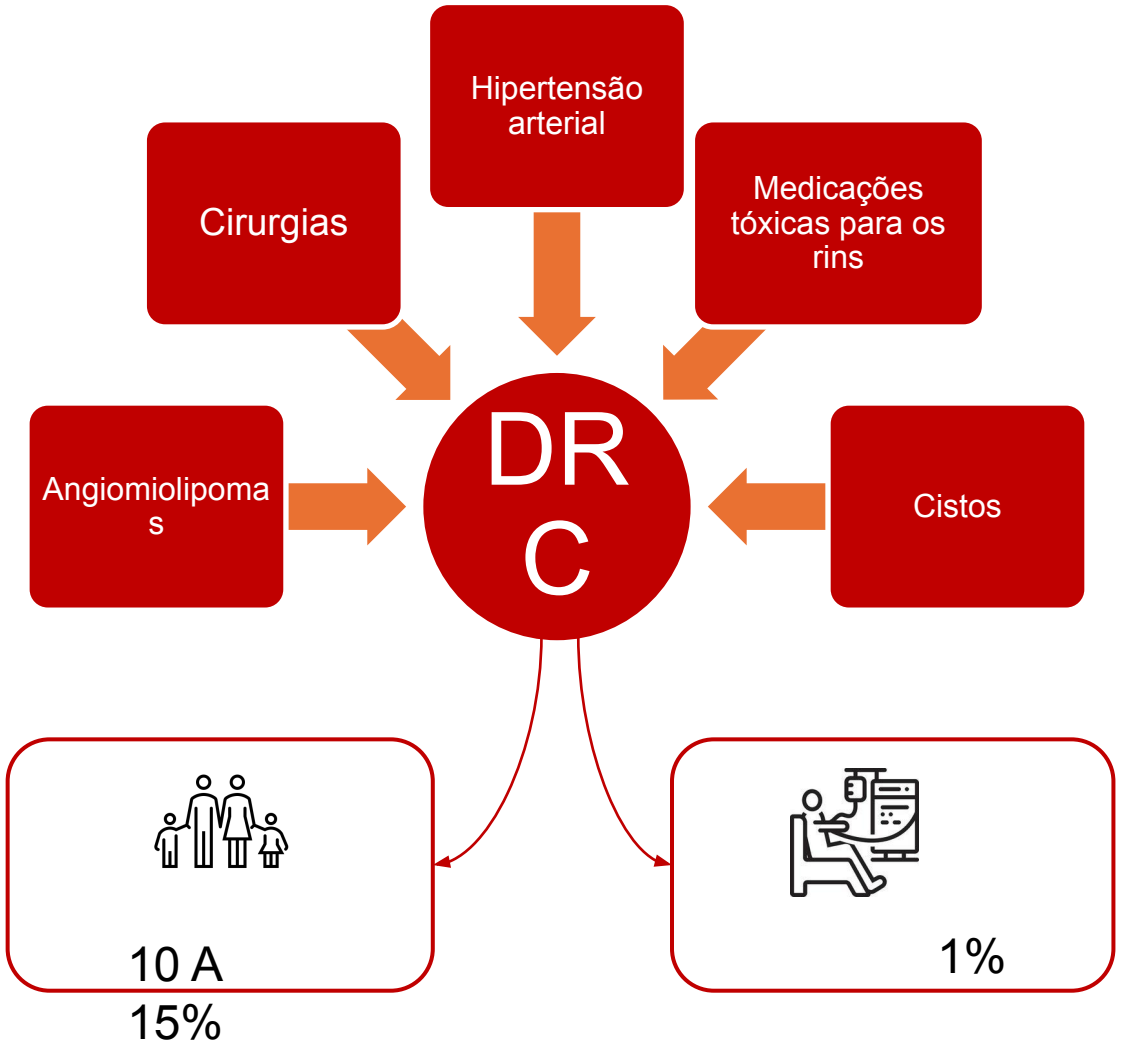


FIGURE 1. Gross radical nephrectomy specimen with concurrent angiomyolipoma (**A**) and renal-cell carcinoma (**C**), clear-cell type, in a patient with tuberous sclerosis. Note the presence of a smaller angiomyolipoma in the opposite pole (***arrow***).

Bissler JJ, Christopher Kingswood J. Am J Med Genet Part C. 2018

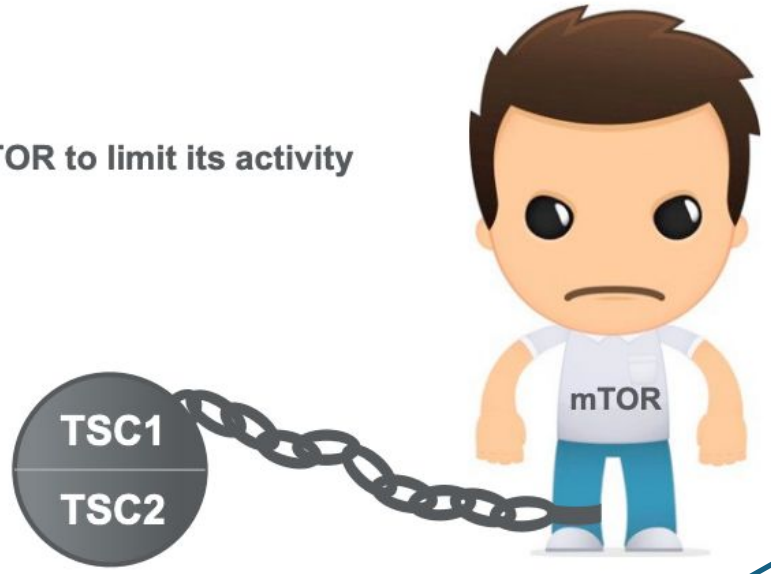
Causas de perda da função renal ?



Bissler JJ, Christopher Kingswood J. Am J Med Genet Part C. 2018

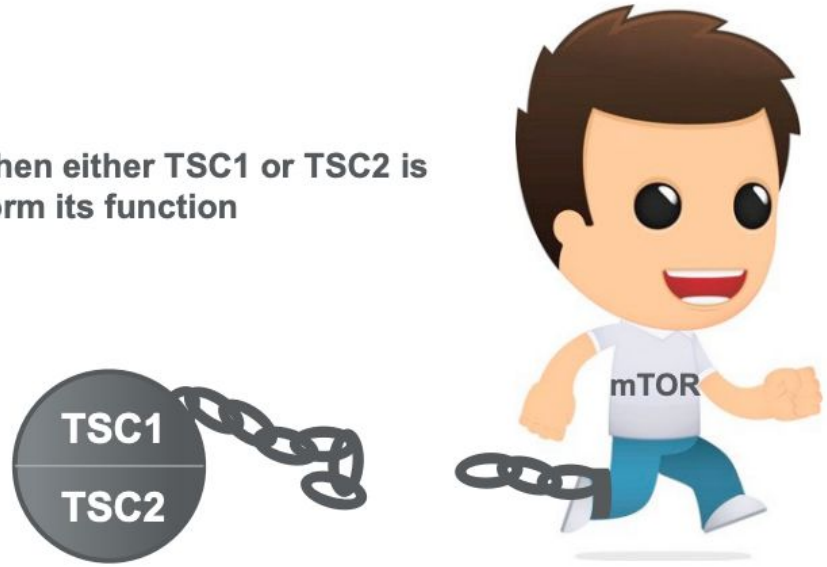
Normal

TSC1 and TSC2 regulate mTOR to limit its activity



TSC

Control of mTOR is lost when either TSC1 or TSC2 is missing or unable to perform its function



Cortesia Darcy Kruguer

TSC + mTOR inhibitor

Control of mTOR is reestablished despite missing or nonfunctional TSC1 or TSC2

Cortesia Darcy Kruguer

Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled tri

Lancet 2013; 381: 817–24

John J Bissler, J Christopher Kingswood, Elżbieta Radzikowska, Bernard A Zonnenberg, Michael Frost, Elena Belousova, Matthias Sauter, Norio Nonomura, Susanne Brakemeier, Petrus J de Vries, Vicky H Whittemore, David Chen, Tarek Sahmoud, Gaurav Shah, Jeremie Lincy, David Lebwohl, Klemens Budde

ACCP
American College of Clinical Pharmacology
Advancing Clinical Care through Pharmacology

Review

Safety Considerations of Mammalian Target of Rapamycin Inhibitors in Tuberous Sclerosis Complex and Renal Transplantation

The Journal of Clinical Pharmacology
2015, 55(4) 368–376

DOI: 10.1002/jcph.428

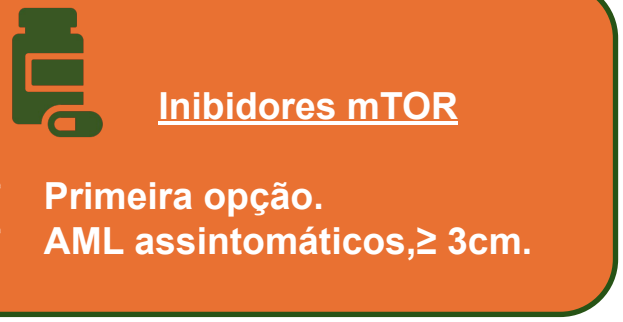
Michael J. G. Somers, MD,[1,2] and Elahna Paul, MD, PhD[2,3]

Nephrol Dial Transplant (2019) 34: 1000–1008
doi: 10.1093/ndt/gfy132
Advance Access publication 19 July 2018

Effect of everolimus on renal function in patients with tuberous sclerosis complex: evidence from EXIST-1 and EXIST-2

John J. Bissler[1], Klemens Budde[2], Matthias Sauter[3], David N. Franz[4], Bernard A. Zonnenberg[5], Michael D. Frost[6], Elena Belousova[7], Noah Berkowitz[8], Antonia Ridolfi[9] and J. Christopher Kingswood[10]

[1]St. Jude Children's Research Hospital and Le Bonheur Children's Hospital, Memphis, TN, USA, [2]Charité Universitätsmedizin, Berlin, Germany, [3]Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, Munich, Germany, [4]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA, [5]Universitair Medisch Centrum Utrecht, The Netherlands, [6]Minnesota Epilepsy Group, St. Paul, MN, USA, [7]Moscow Research and Clinical Institute of Pediatrics, Moscow, Russian Federation, [8]Novartis Pharmaceuticals, East Hanover, NJ, USA, [9]Novartis Pharmaceuticals S.A.S., Rueil-Malmaison, France and [10]Royal Sussex County Hospital, Brighton, UK



RESEARCH ARTICLE

Everolimus long-term use in patients with tuberous sclerosis complex: Four-year update of the EXIST-2 study

John J. Bissler[1]*, J. Chris Kingswood[2], Elzbieta Radzikowska[3], Bernard A. Zonnenberg[4], Elena Belousova[5], Michael D. Frost[6], Matthias Sauter[7], Susanne Brakemeier[8], Petrus J. de Vries[9], Noah Berkowitz[10], Maurizio Voi[10], Severine Peyrard[11], Klemens Budde[8]

PLOS ONE | https://doi.org/10.1371/journal.pone.0180939 August 9, 2017

Li *et al. Orphanet Journal of Rare Diseases* (2019) 14:39
https://doi.org/10.1186/s13023-019-1012-x

Orphanet Journal of Rare Diseases

REVIEW Open Access

Efficacy and safety of mTOR inhibitors (rapamycin and its analogues) for tuberous sclerosis complex: a meta-analysis

Min Li[1,2†], Ying Zhou[1†], Chaoyang Chen[1], Ting Yang[1], Shuang Zhou[1], Shuqing Chen[1], Ye Wu[3] and Yimin Cui[1,2*]

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sirolimus for Angiomyolipoma in Tuberous Sclerosis Complex or Lymphangioleiomyomatosis

John J. Bissler, M.D., Francis X. McCormack, M.D., Lisa R. Young, M.D., Jean M. Elwing, M.D., Gail Chuck, L.M.T., Jennifer M. Leonard, R.N., Vincent J. Schmithorst, Ph.D., Tal Laor, M.D., Alan S. Brody, M.D., Judy Bean, Ph.D., Shelia Salisbury, M.S., and David N. Franz, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

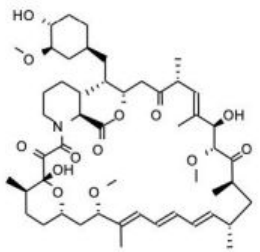
Everolimus for Subependymal Giant-Cell Astrocytomas in Tuberous Sclerosis

Darcy A. Krueger, M.D., Ph.D., Marguerite M. Care, M.D., Katherine Holland, M.D., Ph.D., Karen Agricola, F.N.P., Cynthia Tudor, P.N.P., Prajakta Mangeshkar, M.S., Kimberly A. Wilson, M.S., Anna Byars, Ph.D., Tarek Sahmoud, M.D., Ph.D., and David Neal Franz, M.D.

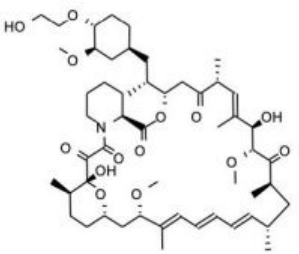
Table 1. Effect of sirolimus treatment on AML size/volume in four open-label trials

	Bissler *et al.* 2008 [1]	Davies *et al.* 2011 [2]	Dabora *et al.* 2011 [3]	Cabrera *et al.* 2011 [4]
	$n = 20$	$n = 16$	$n = 36$	$n = 17$
Patients	6: TSC only	7: TSC only	15: TSC only	all TSC only
	8: TSC + LAM	3: TSC + LAM	21: TSC + LAM	
	6: sporadic LAM	6: sporadic LAM		
Inclusion criterion	≥1 AML ≥1 cm	≥1 AML ≥2 cm	≥1 AML ≥2 cm	≥1 AML >2 cm
Maintenance sirolimus troughlevel (ng/mL)	1–5 in 1	3–6 in 12	3–15	4–8
	10–15 in 19	6–10 in 4		
End point	Total AMLs volume (MRI)	Total AMLs size[a] (MRI)	Total AMLs size[a] (MRI)	Volume of the largest AML (MRI)
Mean decrease in AML volume/size at 12 months	47% in volume	39% in size	30% in size	66% in volume

[a]As defined by the sum of the longest diameters of all target AMLs.



Sirolimus



Everolimus

Pirson Y. Nephrol Dial Transplant, 2013.

Redução do tamanho dos angiomiolipomas !

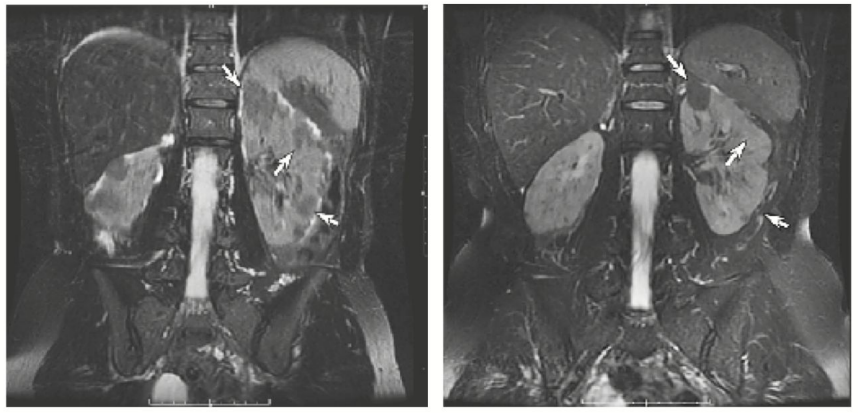


Figure 3. Renal Angiomyolipomas in the Abdomen of a Patient with the Tuberous Sclerosis Complex.

Bilateral angiomyolipomas are shown at baseline and after 12 months of sirolimus therapy. Three lesions in the left kidney are identified by arrows; at 12 months, the top lesion had become reduced in size and the bottom two had become imperceptible. The images were obtained with the use of fast spin–echo T_2-weighted magnetic resonance imaging with fat suppression.

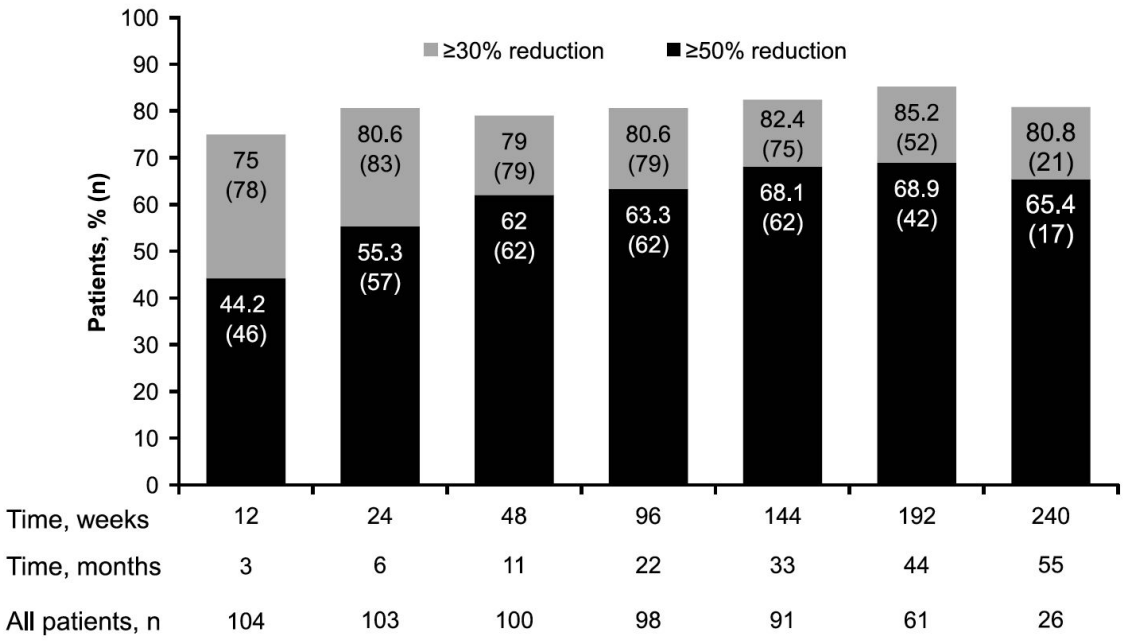
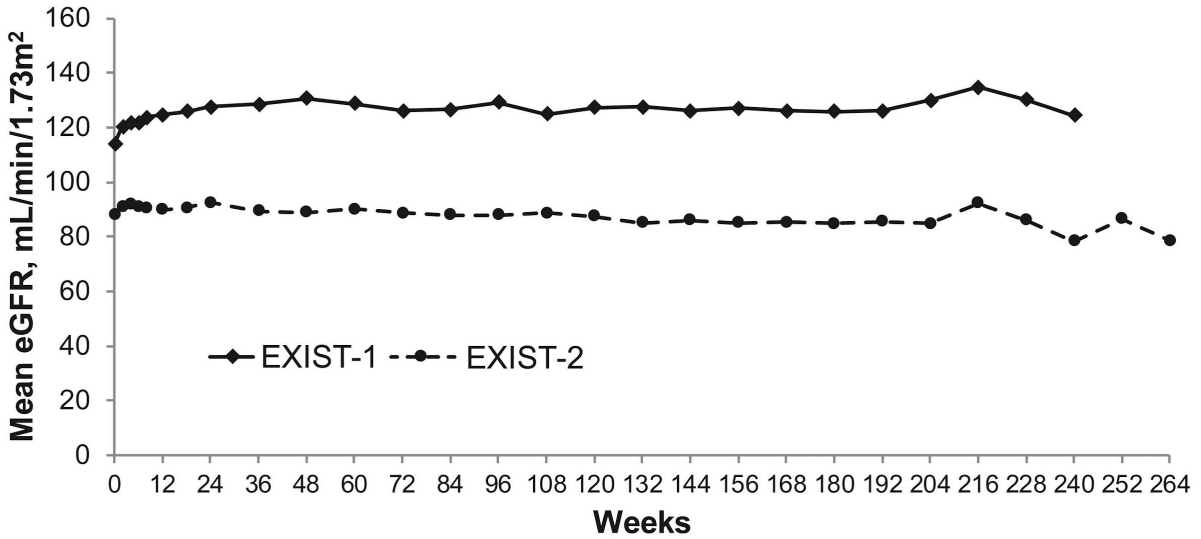


Fig 3. Renal angiomyolipoma response rate with everolimus over time.

Bisller JJ et al. PLOS One 12(8), e0180939 , 2019.

Bissler JJ et al. N Engl J Med. 2008

Função renal não é afetada pelo tratamento com imTOR!



EXIST-1, n	110	104	101	101	102	100	98	97	97	93	93	90	88	84	69	65	63	47	30	20	8		
EXIST-2, n	110	107	104	102	97	100	100	95	95	97	95	93	89	83	68	65	64	46	24	17	11	8	4

Bissler JJ et al. Nephrol Dial Transplant. 2019

Princípais eventos adversos !

Quadro 2 Principais efeitos adversos relacionados ao uso dos inibidores de mTOR sirolimus e everolimus

	Everolimus	Sirolimus
Infeccioso	Trato respiratório superior, infecção do trato urinário, pneumonia	Trato respiratório superior, pneumonia, celulite, infecção urinária
Hematológico	Leucopenia, anemia	Leucopenia, anemia
Metabólico	Dislipidemia, hipofosfatemia	Dislipidemia, hipocalemia
Neurológico	Cefaleia, convulsão	Cefaleia, tontura, tremor
Gastrointestinal	Estomatite, dor abdominal, náusea, vômito	Estomatite, diarreia, náusea e dor abdominal
Dermatológico	Acne, eczema	Acne, foliculite
Ginecológico	Amenorreia, irregularidade menstrual	Amenorreia, irregularidade menstrual
Geral	Artralgia, fadiga	Edema periférico, fadiga
Laboratorial	Aumento na LDH	Aumento de LDH, TGO e TGP
Renal	Proteinúria	Proteinúria
Cardíaco		Taquicardia, pressão arterial elevada

**LDH: enzima lactato desidrogenase; TGO: transaminase glutâmico-oxalacética; TGP: transaminase glutâmico-pirúvica.*

Monich AG, Bissler JJ, Barreto FC. J Bras Nefrol. 2024

Não somos todos iguais: rumo à individualizacão terapêutica.

Gu *et al. Orphanet J Rare Dis* (2021) 16:277
https://doi.org/10.1186/s13023-021-01913-2

Orphanet Journal of Rare Diseases

RESEARCH Open Access

Sequential everolimus for angiomyolipoma associated with tuberous sclerosis complex: a prospective cohort study

Liangyou Gu[1†], Cheng Peng[1†], Fan Zhang[1], Cunjin Fang[2] and Gang Guo[1*]

Methods: In this prospective cohort study, patients met the inclusion criteria received standard or sequential treatment according to their willingness. All patients received an initial dose of everolimus (10 mg oral, once a day) for 3 months. The standard treatment group maintained 10 mg QD for 12 months, while the sequential treatment group reduced the dose to 5 mg QD from the 4th month. The efficacy, serum everolimus concentration and safety were evaluated at 1, 3, 6, 9 and 12 months after treatment. The primary efficacy endpoint was the proportion of patients with confirmed angiomyolipoma response of at least a 50% reduction in the total volume of target AML relative to baseline.

Results: Between June 1, 2016 and June 1, 2017, a total of 53 patients were included. Twenty-three patients received standard treatment, 30 patients received sequential treatment. At 1, 3, 6, 9 and 12 months after treatment, the proportion of patients whose total target tumor volume decreased by ≥ 50% from baseline was 39.1% versus 36.7%, 43.5% versus 56.7%, 47.8% versus 50%, 47.8% versus 60% and 47.8% versus 23.3% respectively ($P > 0.05$ for all). The overall response rate of skin lesions in the two groups was 40.4%, and the response rates of skin lesions at different times were similar for two groups ($P > 0.05$ for all). Major adverse effects (AEs) included mouth ulceration, hypertriglyceridemia, hypercholesterolemia, menstrual disorders. There was no significant difference between the two groups in the incidence of AEs at 3 months after treatment. The incidence of overall and grade 3/4 AEs at 12 months after treatment were significantly lower in the sequential treatment group. The average direct cost of the two groups in 12 months was $15,466 and $11,120, respectively.

Conclusions: Compared to standard treatment, sequential treatment was equally effective, with a lower incidence of adverse events and a lower direct cost, suggesting that it may be an alternative treatment for AML associated with TSC.

ERA CKJ Clinical Kidney Journal

Individualized everolimus treatment for tuberous sclerosis-related angiomyolipoma promotes treatment adherence and response

Everolimus is an alternative to embolization and nephrectomy for managing TSC–AML.

Methods

Setting
Yorkshire and Humber

Time period
Nov 2016–Jun 2021

Study size
28 started on everolimus (10mg/dose)

Monitoring
Serial MR/CT of target AML
Trough levels

Results

68% tolerated for ≥ 3 months

STOP **40%** discontinued due to **42%** recurrent infection, **25%** allergic reaction

68% had dose adjusted from 10mg due to **47%** adverse events, **15%** minimal AML response, **38%** low trough levels

100% reduction in target AML volume

3D volumetric measurements **superior** to 2D measurements of lesion diameter

Conclusion: Everolimus promoted AML regression in all patients taking the drug for > 6 months with stabilisation observed over 3 years. Dose titration maximized responsiveness and minimized side-effects.

Chung, N.K.X. et al.
Clinical Kidney Journal (2022)
a.ong@sheffield.ac.uk @Ong_Lab
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The Journal of Pediatrics
Volume 187, August 2017, Pages 318-322.e2

Clinical and laboratory observations

Improvement in Renal Cystic Disease of Tuberous Sclerosis Complex After Treatment with Mammalian Target of Rapamycin Inhibitor

Brian J. Siroky PhD [1 2], Alexander J. Towbin MD [3], Andrew T. Trout MD [3], Hannah Schäfer MD [4], Anna R. Thamann MPhil [1], Karen D. Agricola MSN, APRN, FNP-BC [2], Cynthia Tudor MSN, CNP [2], Jamie Capal MD [2], Bradley P. Dixon MD [1], Darcy A. Krueger MD, PhD [2], David N. Franz MD [2]

BMC Nephrology

BMC Nephrol. 2024 Oct 24;25:376. doi: 10.1186/s12882-024-03743-3

Everolimus on cystic kidney disease burden reduction in pediatric tuberous sclerosis complex patients: a case series

Sumona Banerjee [1,✉], Louis Richard Feldenberg [2,✉]

nature reviews nephrology

https://doi.org/10.1038/s41581-024-00818-0

Consensus statement

Check for updates

Clinical practice recommendations for kidney involvement in tuberous sclerosis complex: a consensus statement by the ERKNet Working Group for Autosomal Dominant Structural Kidney Disorders and the ERA Genes & Kidney Working Group

Djalila Mekahli[1,2] ✉, Roman-Ulrich Müller[3,4,5], Matko Marlais[6], Tanja Wlodkowski[7], Stefanie Haeberle[7], Marta López de Argumedo[8], Carsten Bergmann[9,10], Luc Breysem[11], Carla Fladrowski[12,13], Elizabeth P. Henske[14], Peter Janssens[15], François Jouret[16,17], John Christopher Kingswood[18], Jean-Baptiste Lattouf[19], Marc Lilien[20], Geert Maleux[21], Micaela Rozenberg[13,22], Stefan Siemer[23], Olivier Devuyst[24,25], Franz Schaefer[7], David J. Kwiatkowski[26], Olivier Rouvière[27,28] & John Bissler[29,30,31] ✉

Box 7

Recommendations on when to initiate mTORC1 inhibition therapy in patients with TSC

Recommendation 1:
We recommend offering mechanistic target of rapamycin complex 1 (mTORC1) inhibition as first-line treatment for angiomyolipomata requiring non-urgent treatment (level A, strong).

Recommendation 2:
In children and adults with tuberous sclerosis complex (TSC), we recommend offering mTORC1 inhibition-based therapy to those with an angiomyolipoma presenting a substantial bleeding risk (Box 5) (level A, strong).

Recommendation 3:
We suggest considering mTORC1 inhibition in all children and adults with TSC and a growing angiomyolipoma of >3 cm in diameter (level D, weak).

Recommendation 4:
We suggest considering immunosuppressive regimens containing a mTORC1 inhibitor in patients with TSC after kidney transplantation based on individual assessment of TSC-associated lesions (level D, weak)

Box 8

Recommendations on dosage of mTORC1 inhibitors

Recommendation 1:
In adults with tuberous sclerosis complex (TSC), we suggest that 5 mg everolimus is a reasonable starting dose and further adaptation is primarily based on side effects and efficacy (level D, weak).

Recommendation 2:
In children with TSC, we suggest that 2.5 mg/m^2 everolimus is a reasonable starting dose and further adaptation is primarily based on side effects and efficacy (level D, weak).

Recommendation 3:
We suggest that dosing schemes might require individualized adaptation (for example, intermittent treatment) (level D, weak).

Recommendation 4:
We recommend dose adjustment of mechanistic target of rapamycin complex 1 (mTORC1) inhibitors in cases of mild adverse events (grade 1 or 2) before discontinuing treatment (level A, strong).

Recommendation 5:
We suggest obtaining everolimus trough levels where safety concerns arise, adherence problems are suspected or lack of efficacy is observed (level A, strong).

Recommendation 6:
We recommend not exceeding everolimus target trough levels of >15 ng/ml (level A, strong).

Statement 1:
Currently available randomized controlled trials examined the effect of everolimus on renal angiomyolipoma in patients with TSC-initiated treatment at a dose of 10 mg/day (EXIST-2, adults) or 4.5 mg/m^2 (EXIST-1, adults and children).

Statement 2:
Sirolimus is a reasonable alternative to everolimus for mTORC1 inhibition in TSC.

Box 10

Recommendations on duration and discontinuation of mTORC1 inhibition therapy in patients with TSC

Recommendation 1:
In cases with response to mechanistic target of rapamycin complex 1 (mTORC1) inhibition, we recommend continuing mTORC1 inhibition therapy for as long as the patient tolerates it (level B, strong).

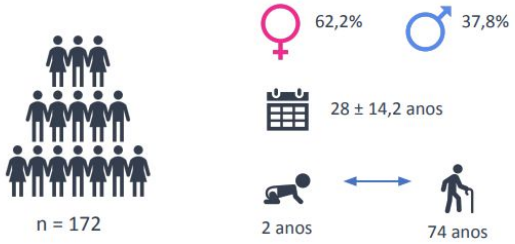
Recommendation 2:
When mTORC1 inhibition therapy has been initiated in cases of typical angiomyolipoma, we recommend continuing for a minimum of 12 months before assessing the response to therapy (level B, strong).

Recommendation 3:
If a typical angiomyolipoma does not respond to mTORC1 inhibition by 12 months, we suggest exploring adherence, dosage and confirmation that the lesion is indeed a typical angiomyolipoma as well as considering alternative treatment options (level D, weak).

Recommendation 4:
We recommend stopping or pausing mTORC1 inhibitor treatment in patients with active severe infection or who experience severe adverse effects (grade ≥3) (level B, strong).

Statement:
The safety profile of mTORC1 inhibition in patients with tuberous sclerosis complex (TSC) does not differ from that in the general population.

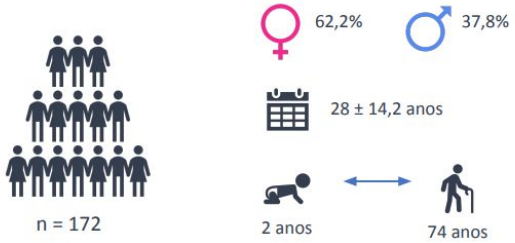
O que sabemos sobre nós mesmos ?
Dados brasileiros: Sempre um desafio !



	Geral	Por faixa etária (em anos)		
		< 18	18 a 39	≥ 40
Angiomiolipomas	143/157 (91,1)	18/30 (60)	93/95 (97,9)	32/32 (100)
Múltiplos	128/137 (93,4)	15/17 (88,2)	85/91 (93,4)	28/29 (96,5)
Bilateralidade	120/139 (86,3)	15/17 (88,2)	81/91(89)	24/31(77)
≥ 30 mm	63/122 (51,6)	5/22 (22,7)	41/76 (53,9)	17/24 (70,8)
Maior angiomiolipoma (mm) [b]	112; (33,5 [19-63])	13; (18 [9-35])	75; (32 [20,5-62,5])	24; (53,5 [25,7-90,5])
Sangramento renal	24/145 (16,6)	1/38 (2,6)	13/80 (16,3)	10/27 (37)
Intervenção cirúrgica e/ou radiológica [#]	46/165 (27,9)	2/37 (5,4)	26/95 (27,4)	18/33 (54,5)
Nefrectomia parcial	33/56 (59)	2/3 (66,7)	22/31 (71)	9/22 (41)
Nefrectomia total	11/56 (19,6)	0	4/31 (12,9)	7/22 (31,8)
Embolização arterial	12/56 (21,4)	1/3 (33,3)	5/31 (16,1)	6 (27,2)
Cistos renais	71/142 (50)	15/29 (51,7)	41/86 (47,7)	15/27 (55,6)
Carcinoma de células renais	5/157 (3,1)	0/30	1/95 (1,05)	4/32 (12,5)

Dados pessoais, não publicados

O que sabemos sobre nós mesmos ?
Dados brasileiros: Sempre um desafio !



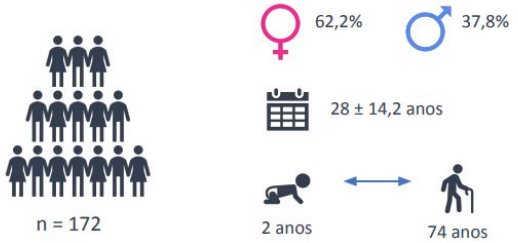
	Geral	Por faixa etária (em anos)		
		< 18	18 a 39	≥ 40
Hipertensão arterial sistêmica	31/152 (18)	4/32 (12,5)	18/92 (19,6)	9/28 (32,1)
PAS (mmHg) [a]	57; (111,8±13,9)	24; (106±12,6)	26; (117,1±13,5)	7; (112,6±13,7)
PAD (mmHg) [a]	57; (71,4±11,6)	24; (64,6±9,7)	26; (77,1±10,6)	7; (73,1±9,8)
Dor lombar	26/145 (17,9)	2/38 (5,2)	18/80 (22,5)	6/27 (22,2)
Hematúria	14/143 (9,8)	2/35 (5,7)	9/82 (11)	3/26 (11,5)
Proteinúria	36/101 (35,6)	2/13 (15,3)	22/64 (34,3)	12/24 (50)
Uso inibidores da via mTOR	61/172 (35,5)	9/39 (23,1)	34/99 (34,3)	18/34 (52,9)

56% pacientes com proteinúria não estavam em uso de imTOR

42% dos pacientes com indicação de uso de imTOR não estavam fazendo uso da medicação ($p < 0.001$)

Dados pessoais, não publicados

O que sabemos sobre nós mesmos ?
Dados brasileiros: Sempre um desafio !



	Geral	Por faixa etária (em anos)		
		< 18	18 a 39	≥ 40
Creatinina (mg/dL) [b]	138; (0,75 [0,61-0,91])	16; (0,51 [0,38-0,59])	91; (0,71 [0,62-0,88])	31; (0,9 [0,77-1,1])
TFGe (ml/min/1,73m^2) [b]	131; (115 [85-130])	9; (154 [138-178])	91; (123 [94-132])	31; (78 [60-104])
Doença renal crônica*	13/131 (9,9)	0/9	6/91 (6,6)	7/31 (22,6)
Estágios de DRC				
G1	95/131 (72,5)	9/9 (100)	74/91 (81,3)	12/31 (38,7)
G2	23/131 (17,5)	0	11/91 (12,1)	12/31 (38,7)
G3a	5/131 (3,8)	0	3/91 (3,3)	2/31 (6,5)
G3b	2/131 (1,5)	0	0	2/31 (6,5)
G4	4/131 (3,1)	0	1/91 (1,1)	3/31 (9,6)
G5	1/131 (0,8)	0	1/91 (1,1)	0
G5-D	1/131 (0,8)	0	1/91 (1,1)	0

Dados pessoais, não publicados

O que sabemos sobre nós mesmos ?
Dados brasileiros: Sempre um desafio !

- ✔ **N= 10; idade: 32,8 ± 9,87 anos; 7 mulheres, 3 homens.**
- ✔ **Em uso da medicação há pelo menos 12 meses; 5 sirolimo, 5 everolimo.**

	Pré tratamento	Pós tratamento	Alteração (%)
Volume renal direito (cm^3)	1195 (183.6 – 4274)	1027 (150 – 5343)	**-14 (-6,6; -30)**
Volume renal esquerdo (cm^3)	736 (184.7 – 1999)	610 (219 – 2203)	**-15 (3,8; -37,4)**
Volume renal total (cm^3)	1370 (257 – 6143)	1078 (415.5 – 2393)	**-13 (-2,7; -30.8)**
Diâmetro do AML (mm)	93 (26 – 187)	81 (20 – 171)	**-13 (- 1,5; -64,3)**
Volume maior lesão direito (cm^3)	1212 (0.42 – 7721.6)	950 (0.38 – 8835.8)	**-25 (-9,5; -64,3)**
Volume maior lesão esquerdo (cm^3)	647 (11.2 – 2077)	110 (5.8 – 1591.8)	**-33 (10,5; -77.4)**

- Efeitos adveros mais comuns:
  - Mucosite, diarreia, dislipidemia, acne.
  - Sem necessidade de suspender a medicação.

Dados pessoais, não publicados

ARTIGO DE REVISÃO

Complexo da Esclerose Tuberosa e rins: o que os nefrologistas devem saber

Tuberous Sclerosis Complex and the kidneys: what nephrologists need to know

Autores

Aline Grosskopf Monich[1,2]

John J. Bissler[3,4,5]

Fellype Carvalho Barreto[1,6]

RESUMO

O complexo da esclerose tuberosa (CET) é uma doença autossômica dominante caracterizada pelo desenvolvimento de hamartomas no sistema nervoso central,

ABSTRACT

Tuberous sclerosis complex (TSC) is an autosomal dominant disease characterized by the development of hamartomas in the central nervous

Obrigado !

UFPR
UNIVERSIDADE FEDERAL DO PARANÁ

abet
Associação Brasileira de Esclerose Tuberosa