Independent PKD1 and TSC2 mutations cause a phenotype different from the typical contiguous gene syndrome

Cristina Cabrera-López[1], Gemma Bullich[2], Jose Ballarín[3], John J Bissler[4], Peter C Harris[5], Elisabet Ars[2], Roser Torra[1]

[1]Inherited Kidney Diseases. Nephrology Department, Fundació Puigvert, Instituto de Investigaciones Biomédicas Sant Pau (IIB-Sant Pau), UAB, REDinREN, IICIII, Barcelona, Spain
[2]Molecular Biology Laboratory, Fundació Puigvert, Instituto de Investigaciones Biomédicas Sant Pau (IIB-Sant Pau), UAB, REDinREN, IICIII, Barcelona, Spain
[3]Nephrology Department, Fundació Puigvert, Instituto de Investigaciones Biomédicas Sant Pau (IIB-Sant Pau), UAB, REDinREN, , IICIII Barcelona, Spain
[4]Pediatric Nephrology Department. Le Bonheur Children's Hospital. Memphis, Tennessee. USA
[5]Department of Biochemistry and Molecular Biology, Mayo Clinic, Rochester, Minnesota; and Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota

Introduction and objectives

Mutations in TSC1 or TSC2 cause the tuberous sclerosis complex (TSC), while mutations in PKD1 or PKD2 cause autosomal dominant polycystic kidney disease (ADPKD). The PKD1 gene lays immediately adjacent (60 bp) to the TSC2 gene, in a tail-to-tail orientation. Deletions involving both genes cause a contiguous gene syndrome characterized by severe ADPKD and TSC No descriptions of patients having both diseases caused by two independent mutations in the PKD1 and the TSC2 genes have been reported to date.

Mutations in TSC1 or TSC2 permit aberrant upregulation of the mTOR signalling pathway causing cellular proliferation. Also, polycystin 1 (PC1), the PKD1 protein product, may interact with tuberin (TSC2 protein product) and hamartin (TSC1 protein product) to suppress mTOR activity.

We report a patient with TSC and ADPKD due to independent mutations in both the TSC2 gene and PKD1 gene who was treated with mTOR inhibitors.

Case report

A 26-year-old man first presented to our renal unit at 11 years of age following detection of cystic kidneys. His father, paternal aunt, paternal grandmother and sister have ADPKD (Figure 1). The age at onset of ESRD was 68 for the grandmother 44 for the father and 48 for the aunt. The patient's sister has normal renal function, hypertension and enlarged kidneys at the age of 30. There is no family history of TSC.

The patient was diagnosed with TSC at 3 months of age due to hypomelanic macules and a seizure. A cardiac rhabdomyoma was removed at 6 months of age. A brain MRI scan showed numerous subependymal nodules and periventricular calcifications. Facial angiofibroma developed in early childhood. An ultrasound scan of the kidneys performed at 3 years of age demonstrated multiple small cysts throughout the renal parenchyma. An AML of 3 cm of diameter in the left kidney was detected at the age of 14. During follow up, cysts increased in size and number and kidney length was 17 cm at 22 years of age. At that time the AML of the left kidney had increased to a diameter of 6 cm. Sirolimus was started at 22 years of age (mean dose: 3 mg/day, trough levels 6.9±3.8 ng/ml). Follow up of AML and kidney volume is shown in table 1 and Figures 2 and 3. At that time, the negative results of two large trials using mTOR inhibitors in ADPKD were released and treatment with sirolimus was discontinued.

Initially linkage analysis showed that the ADPKD family was linked to the PKD1 gene (Figure 1). Sequencing of PKD1 and TSC2 disclosed: a deletion of PKD1 (exons 1-10): c.1-?_2097+?del, (p.Met1fs) and a TSC2 nonsense mutation: TSC2 c.2251C>T (p.Arg751*)

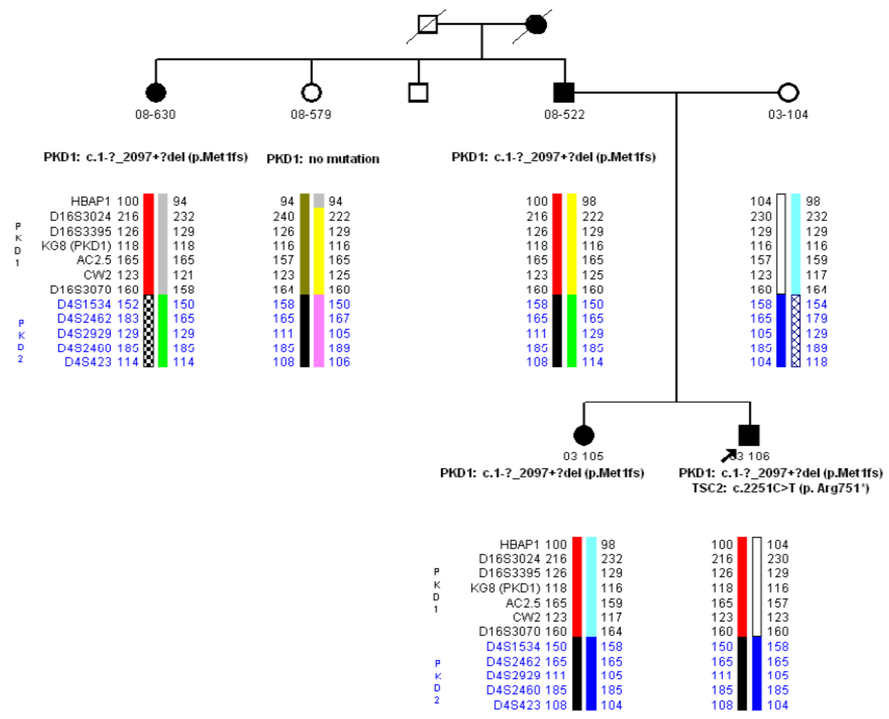

Figure 1: Pedigree of the family showing the segregation analysis of haplotypes as well as *PKD1* and *TSC2* mutations. The arrow points the proband reported in this case

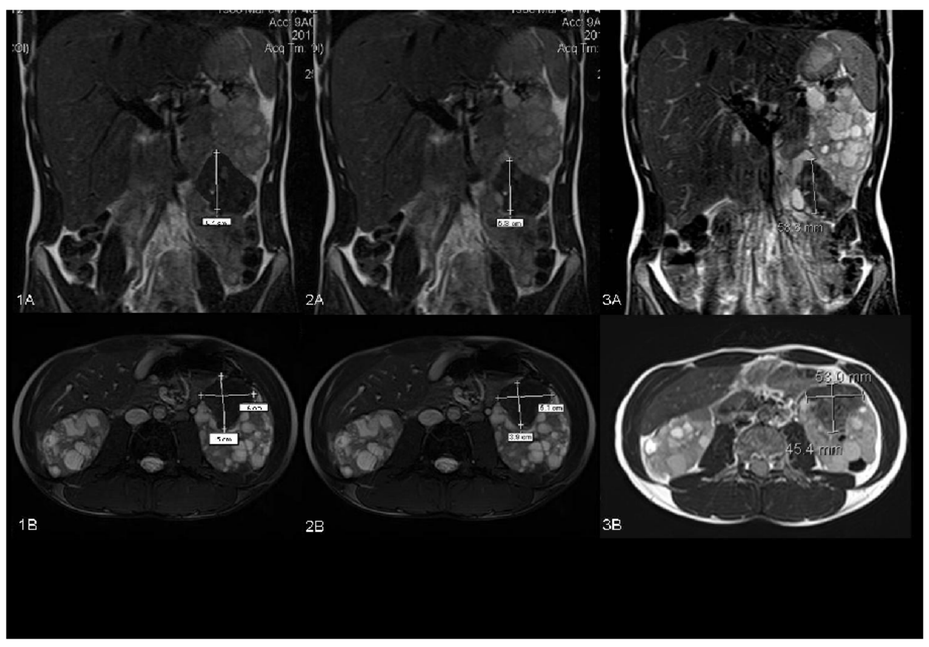

Figure 2: AML volume evolution: 1A and 1B baseline; 2A and 2B at the end of 3 years treatment with mTOR inhibitors; 3A and 3B one year later (without treatment). The AML decreased in size after three years on treatment and slightly increased in size one year after treatment withdrawal.

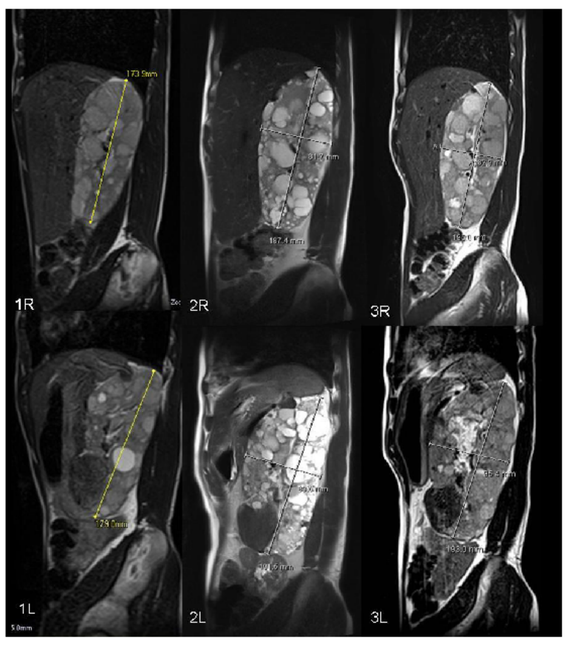

Figure 3: Right (top row) and left kidney (bottom row): initial MR (1R and 1L), after three years on treatment with mTOR inhibitors (2R and 2L) and one year later (without treatment) (3R and 3L).

	Basal	6 months	12 months	24 months	36 months	48 months
AML volume (ml)	99,8	69,7	54,8	54,8	68,2	73
Kidney volume (ml)						
right kidney	714,7	646,5	637,7	625,1	780	857,8
left kidney	712	678,4	673,7	682,5	875,4	953,4
bilateral kidney volume	1426,7	1324,9	1311,4	1307,6	1655,4	1811,2
Laboratory tests						
creat (mmol/l)	72	86	96	86	96	102
MDRD4	90	90	84	90	82	76
alb/creat	12,54	23,99	24,93	25,89	19,2	6,5
cholesterol mmol/l)	3,2	3,84	4,21	4,26	4,1	3,86
tryglicerides (mmol/l)	0,61	0,81	1,17	0,63	0,87	0,96

Table 1: Shaded colours: on treatment. Blank off treatment

Discussion

A single individual carrying mutations in two different genes causing two different diseases, and therefore suffering both entities, is not frequent but depends on the prevalence of each disease: chances of having ADPKD are ~1/800 and TSC ~1/8000 →possibility that a patient carries independent mutations in a PKD and TSC gene: 1/6 million.

Children with PKD1/TSC2-CGS usually enter ESRD in the second or third decade of life. If the CGS phenotype were just due to an additive effect of disrupting both genes, one would expect the same effect of a truncating mutation in both genes than a deletion involving both of them. However, this case show an apparent limited impact of carrying a *TSC2* mutation in addition to the *PKD1* one opposite to PKD1/TSC2-CGS.

Conclusions

- The phenotypes associated with independent deletion of each of the contiguous genes are different and the contiguous syndromes represent an accumulation of these phenotypes.
- mTOR inhibition reduced AML volume as well as kidney volume during the first two years, but renal function declined. Both AML and renal volume increased during the third year even while on the treatment and adequate Rapamycin plasma levels.
- This case reveals that although *PKD1* and *TSC2* are adjacent genes and that tuberin, hamartin and PC1 may cross-talk and regulate mTOR inhibition, having independent mutations in *TSC2* and *PKD1* does not necessarily give rise to the typically severe PKD1/TSC2-CGS phenotype. It also confirms that mTOR inhibitors are efficient in reducing AML and ADPKD kidney volume, but do not have a positive impact on renal function.

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Fundació Puigvert C/Cartagena, 340 08025 Barcelona. **Tel.** 934169700 **Fax.** 934169730 **web.**www.fundaciopuigvert.es **mail.** rtorra@fundacio-puigvert.es

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D) Genetic diseases and molecular genetics.

ROSER TORRA

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