Not all renal cysts are created equal

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In December, 2008, a 55-year-old woman presented to us with gross haematuria and dysuria. She reported passing a "stone" and had been diagnosed with a urinary tract infection which was treated with ciprofloxacin for a week before presentation. Before admission, ultrasonography to investigate right flank pain had shown bilateral renal cysts; at this time her creatinine was normal at 71 µmol/L, and bicarbonate was low at 20 mmol/L; serum anion gap was normal. She had a history of nephrolithiasis and bipolar disorder, which had been treated with lithium for 20 years. When her father was 36 years of age he developed renal failure necessitating kidney transplantation; unfortunately his medical records were no longer available. No other family members had kidney disease. In view of her family history and sonographic findings, she had been presumptively diagnosed with autosomal dominant polycystic kidney disease and lithium treatment had been stopped. On presentation to us, we did an MRI (figure) which showed bilateral, mainly sub-centimetre, renal cysts and normal sized kidneys; left 10·2 cm, and right 11·0 cm.

Autosomal dominant polycystic kidney disease is caused by mutations in two distinct genes, PKD1 on chromosome 16 and PKD2 on chromosome 4. Our patient did not have truncating mutations, although these mutations are only found in around 60% of patients.[1] Several other features also prompted us to consider other diagnoses, including simple cysts, medullary sponge, or medullary cystic disease. Radiographic appearance of the kidneys was not typical of autosomal dominant polycystic kidney disease; a cardinal feature is enlarged kidneys with cysts of varying sizes,[1] whereas our patient had normal sized kidneys with sub-centimetre cysts. Also, she was not hypertensive, which is unusual for a 55-year-old person with the disorder. A salient clue to the likely cause of renal cysts in our patient was her history of long-term lithium use. Histological analysis of renal biopsies from patients treated with lithium have shown chronic tubulointerstitial nephropathy characterised by tubular atrophy and interstitial fibrosis interspersed with small medullary and cortical cysts of distal or collecting tubule origin. MRI is the most sensitive method for detection of renal microcysts associated with lithium.[2] Distinguishing features include small to normal sized kidneys with multiple microcysts typically ranging from 1 mm to 2 mm and rarely larger than 3 mm. On the basis of the MRI findings, we diagnosed our patient with renal microcysts associated with lithium. At last follow-up in May, 2010, our patient was well, her creatinine was 123 µmol/L, and she had not had any psychiatric symptoms since stopping lithium.

The characteristic MRI appearance of lithium-induced nephropathy makes it a useful way to confirm chronic lithium toxicity; gadolinium administration is not required. The most important risk factor for lithium-induced nephropathy is long-term use; therefore if renal disease is suspected it is advisable to substitute lithium with another agent. However, discontinuation of lithium might not reverse continued deterioration in renal function.[3] Why lithium treatment causes renal cysts is unknown, but the same abnormalities have also been seen in rodents treated with lithium.[4] Lithium is frequently used in the laboratory setting to enhance signalling via the canonical *Wnt*/β-catenin pathway. Persistent activation of this pathway in mice is associated with polycystic kidney disease.[5] Lithium inhibits glycogen synthase kinase-3 beta, which prevents degradation of β-catenin resulting in increased transcription of canonical *Wnt* target genes. Although canonical *Wnt* signalling is required for normal renal development, persistent activation results in renal cysts. Whether this pathway underlies cyst formation in human beings taking lithium requires further study.

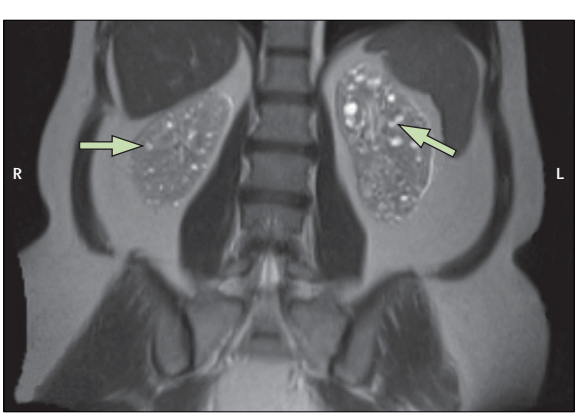

Figure: **Coronal T2 MRI of abdomen**
Normal sized kidneys and numerous small cysts (arrows) distributed throughout the renal parenchyma.

Contributions
MGA looked after the patient, SS collected the data, MGA and TW analysed and interpreted the data, and all authors wrote the report. TW is supported by NIH grant DK076017.

Conflict of interest
TW holds *PKD1* testing patent and TW and spouse are entitled to a share of royalty received by the University on sales of products described in this article: they have elected to donate their share of the royalty to the Polycystic Kidney Disease Research Foundation.

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