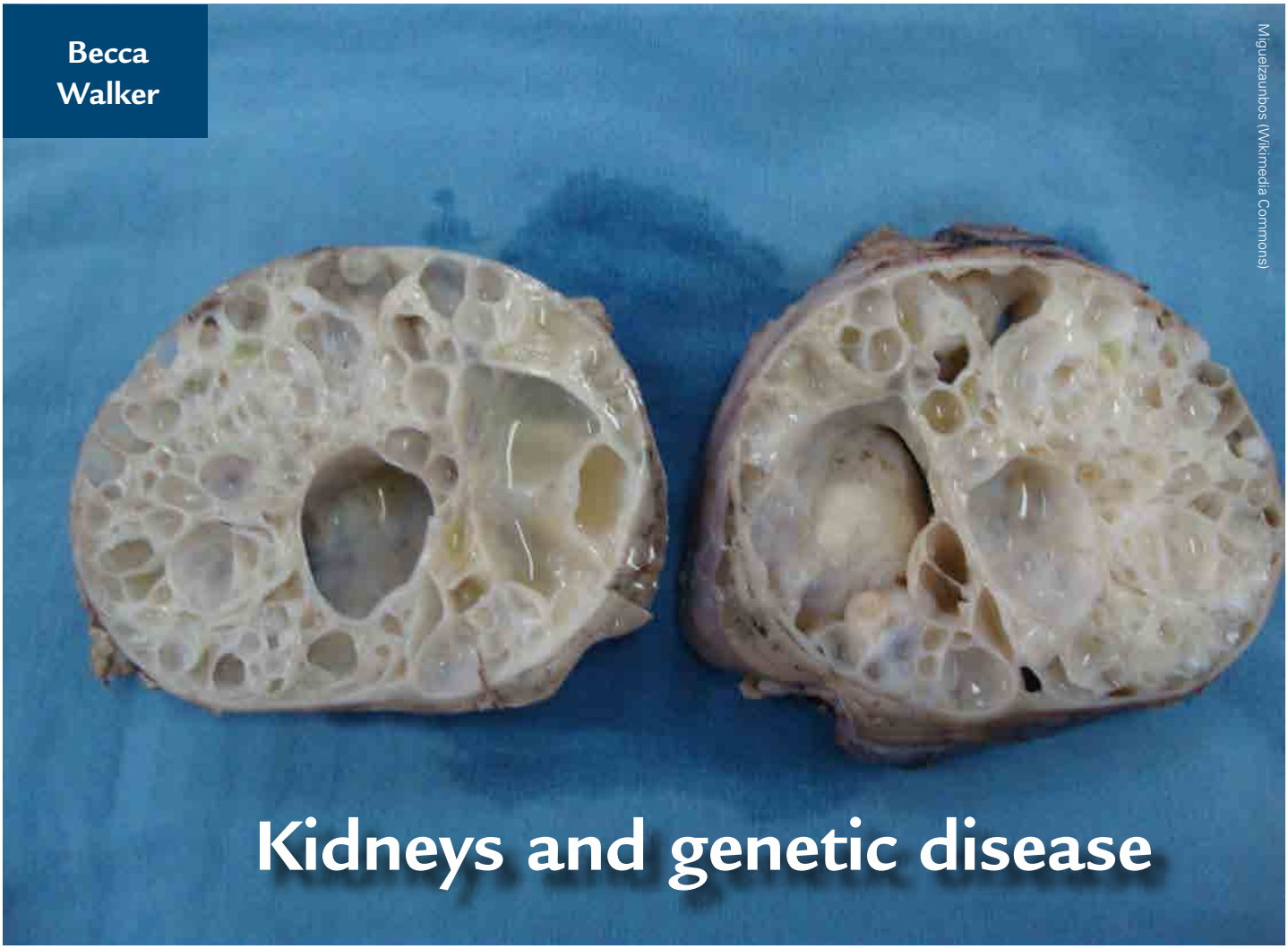
Becca Walker



Kidneys and genetic disease

Key words
kidney disease
genetic disease
inheritance
dialysis

Cross-section of kidneys affected by cysts; this is the recessive form of the disease.

The kidneys are essential organs which provide a remarkable service to the body. You may know that the kidneys filter the blood and make urine but did you know that they also produce hormones, regulate blood pressure and water retention, participate in the production of red blood cells and activate vitamin D to keep your bones healthy? With so many functions, it is easy to see how catastrophic it would be if your kidneys stopped working.

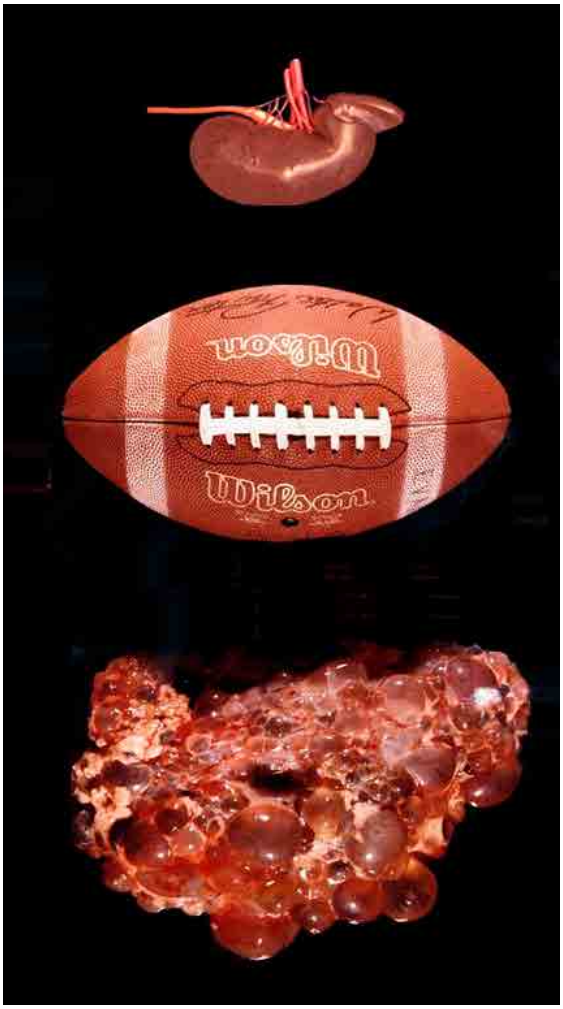
My research for the past four years has been focused on a disease where the kidneys gradually fill with cysts and stop working. My particular interest involves understanding how gene mutations cause changes in proteins which in turn lead to cyst development.

What is ADPKD?

'Renal' means relating to the kidneys.

Autosomal Dominant Polycystic kidney disease (ADPKD) is a common yet devastating disease. It affects 1 in 400-1000 people worldwide. ADPKD is the most common genetic renal disorder. The disease is characterised by the development of cysts throughout the kidney tubules which enlarge and eventually overtake the kidney structure. These cysts destroy renal function, often resulting in renal failure by the patient's sixth decade of life. An individual cyst can expand to be 10 cm in diameter – the size of a normal adult kidney.

The author looking at a slide of a mouse kidney to check for cysts



An end-stage ADPKD kidney gradually develops cysts which overtake the kidney structure. Normally, your kidney is the size of your fist yet with ADPKD, each kidney can increase to the size of an American football, making the patient appear pregnant. Image adapted from original by Dr Andrew P. Evan, Indiana University School of Medicine.

The kidney is a remarkable organ, able to overcome a great deal of structural damage. When cysts start to develop, the affected kidney tubules increase filtration in a process known as super-filtration, in order to compensate for the tubules which become blocked. Because of this, kidney function is maintained at a normal level while the kidney is filling with cysts. At a critical point, the kidney can no longer compensate and function rapidly declines towards renal failure.

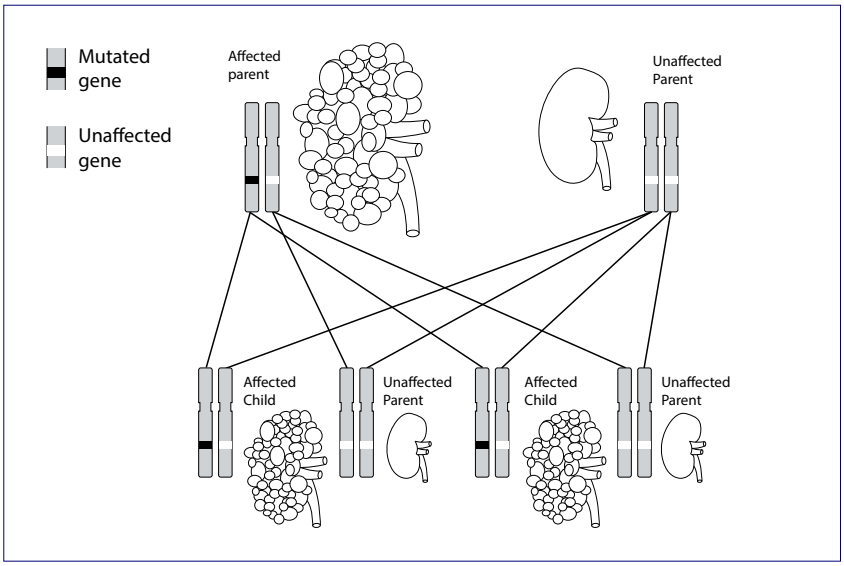
ADPKD numbers

ADPKD...

- affects 1:400-1000 people worldwide
- affects 60 000 people in the UK
- accounts for 1 in 8 people with a transplant kidney
- accounts for 1 in 10 patients on dialysis

Genetics of ADPKD

ADPKD is an inherited disease. A patient will have inherited a single mutated copy (called an allele) of either the PKD1 or PKD2 gene from an affected parent. A mutated allele is passed from an affected parent to a child at the rate of one in two. Therefore, children of an affected parent have a 50:50 chance of developing the disease. This pattern of inheritance is how the disease became known as autosomal dominant, meaning that the mutation occurs in a gene on a chromosome which is not a sex chromosome (X or Y) and one mutated copy is sufficient to cause the disease.



A mutated copy of either PKD1 or PKD2 is passed on to children at the rate of 1:2 from an affected parent. Since ADPKD is an inherited disease, patients often have a long line of affected family members.

Since there is often a positive family history, a genetic test is often not necessary to confirm the presence of the disease. Diagnosis is typically by ultrasound or CT scan but this will not tell the patient how quickly the disease is likely to progress. A patient will be continually monitored throughout their lifetime to keep a close eye on their renal health.

PKD1 mutations are more common than PKD2 mutations and tend to have a more severe progression. However, there is wide variation in the severity and progression of the disease, even between members of the same family who have the same mutation. This could be due to a number of reasons including environmental factors such as diet.

Interestingly, unlike many diseases in ADPKD there is not a common mutation that a large number of patients inherit. Each affected family tends to have a unique mutation and there is often a high level of variation in progression even within these families. Since there are such a high number of different mutations it is hard to pinpoint the effect of a specific mutation on the progression of the disease. Understanding the way a specific mutation contributes to patient disease progression can help us to predict the best way to treat the patient.

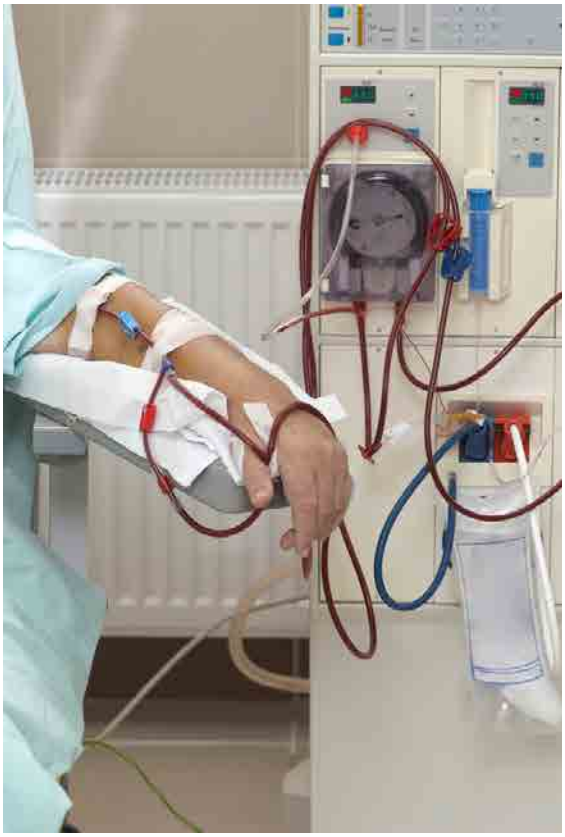
Ștefan Báthory, the sixteenth century king of Poland, had the first documented case of ADPKD.

The first documented case of ADPKD dates back to the 16th century when Ștefan Báthory (1533-1586) the king of Poland, was autopsied. The kidneys of the king, who killed Ivan the Terrible, were described as being 'large like those of bull, with uneven and bumpy surface.' Yet, despite being first reported five centuries ago, ADPKD is still considered untreatable, the mechanisms behind the development of cysts are relatively poorly understood and the clinical outcome is poor. In recent years however, significant research has been undertaken to understand the mechanisms of cyst development and the effects of drugs in preventing the progression of the disease.

Progress in treatment

Recently, a great step forward in the treatment of ADPKD was made. The first drug to slow the progression of ADPKD was approved for use in the UK. In a three year long clinical trial, Tolvaptan was found to significantly reduce the speed of kidney volume increase when compared to patients who were given placebos.

For a drug to go all the way from the first stages of development to being successfully approved for patient use is both unusual and time consuming. There are several phases of clinical trials, all of which a drug must pass. After having built up the understanding of the disease mechanisms, potential drugs are tested on animal models in preclinical trials to understand the toxicity and safety of the drug. The first phases of drug trials are undertaken on a small group of healthy volunteers before the drugs are tested on patients to assess side effects, safety and effectiveness of the drug.



Kidney dialysis is a process of purifying the blood of a person whose kidneys are not working normally. The blood comes out of the body, through a dialysis machine and is then returned to the body.

Clinical trials

Many drugs are assessed for decades but fail to pass clinical trials and therefore are not fit for use on humans. A way to speed up the process of these trials is to repurpose a drug that has already been approved to work for another condition. In this way a drug can bypass much of the early stages of research and go straight to clinical trial. This means that the time for a drug to be approved for patients is greatly reduced.

Tolvaptan was previously approved for used in heart failure after trials in 1998 for patients in Japan. Having been repurposed, a number of the side effects were known, but another round of clinical trials was undertaken to assess the effectiveness of the drug for treating ADPKD. Nearly two decades passed between Tolvaptan being first used in patients and being approved for treatment of ADPKD. With time we will gain more understanding of how to enhance the positive effects of Tolvaptan and increase patient survival.

Despite recent progress in the field, there are still a number of areas underlying the development of the disease which remain unclear. Studies undertaken at the first level of basic research, such as the work that I have undertaken, are essential to the progression of the field and will eventually impact on patient survival.

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