EVA VAZQUEZ FOR *NATURE*

Kidney genes

Evidence that genetics plays a major part in chronic kidney disease is changing how the disease is diagnosed and prevented. **By Bianca Nogrady**

Andrew Mallett was training to be a kidney specialist at the Royal Brisbane and Women's Hospital in Australia in 2011 when he met an 18-year-old man whose kidneys were on the verge of collapse. Struck by how unusual this condition was in an otherwise fit, healthy young person, Mallett asked if anyone else in the man's family had kidney problems.

"It turned out his brother, who was three years younger, had a kidney transplant; his mum had had a kidney transplant, his uncle was on dialysis, and his grandmother had kidney disease, so there was this massive family history," says Mallett, now a nephrologist at the Institute for Molecular Bioscience at the University of Queensland in Brisbane. But the family and their physicians didn't know what type of kidney disease they had.

At the time, genetic sequencing was still in its early days, and had failed to provide answers. Then a chance meeting with a researcher studying mitochondrial mutations in kidney disease — in which the disease-linked genetic variant is found in the mitochondrial DNA, which is inherited only from the mother — prompted Mallett to suggest that the man and his family were candidates for the study. The genetic test came back positive. Although this information did not yet open the door to a treatment approach, it did finally give the family an understanding of why so many of them were affected — and reassured the man that he would not pass the disease on to future generations.

Paediatric nephrologist Cathy Quinlan, from the Melbourne Genomics Health Alliance in Australia, estimates that genetic testing has a significant impact in around a half of people with kidney disease. "It changes their treatment, or it might be that it changes something with the transplant pathway," she says. A genetic diagnosis can also alert clinicians to other possible effects of that variant, such as hearing loss and eye problems.

Once a tool only for research, genome sequencing is now being used by clinicians to identify the cause of chronic kidney disease (CKD), to guide treatment, advise family members and provide reproductive genetic counselling. It's also being used to screen people with suspected kidney disease or even the general population, allowing physicians to intervene earlier in the course of the disease and delay — or even avoid — the worst outcomes.

An unfortunate inheritance

Around two-thirds of cases of chronic kidney disease are caused by diabetes or high blood pressure, and lifestyle factors such as smoking, and being overweight or obese, are commonly linked to the disease. The role of genetics is less well understood — but researchers know it plays a part.

"If you ask anybody who has kidney disease, about a third of patients will tell you that they have a family member who also has some form of kidney disease," says Ali Gharavi, a kidney specialist with a focus on genetics at the Columbia University Institute for Genomic Medicine in New York. The disease is also more prevalent among people of certain ethnicities, including African American, Hispanic and sub-Saharan African populations. Although in the past this prevalence had been attributed to social determinants of health, Gharavi says that

there's now a greater awareness that genetic factors also contribute.

Certain well-characterized genetic variants are known to contribute substantially to the risk of CKD in an individual. One such group are mutations in the *COL4A1* gene, which is linked to Alport disease — an inherited condition characterized by kidney, hearing and eye problems and that can be brought about by a single mutation. Other monogenic mutations directly linked to CKD are found in the *PKD1* or *PKD2* genes that are linked to polycystic kidney disease, and in the *APOL1* and *HNF1B* genes. So far, around 500 single genes have been identified that are strongly associated with the development of CKD, especially in children.

Gharavi estimates that around one in 10 people with CKD can trace their condition back to a single mutated gene. Among children, this figure could be much higher, says Afshin Parsa, a nephrologist at the National Institute of Diabetes and Digestive and Kidney Diseases in Bethesda, Maryland. "You might have 50–60% that have a genetic cause," he says.

There are also more than 1,000 other genetic variants that are known to influence the risk of CKD, but which might have only a small effect on risk in an individual. These variants don't act in isolation, but rather interact with each other and with non-genetic risk factors, such as co-morbidities and lifestyle factors, to increase the risk of disease.

In both the monogenic and polygenic scenarios, the presence of a variant doesn't mean that an individual will develop severe CKD — or that they will develop the disease at all. The disease could manifest at any time from early childhood to late adulthood.

Tuning up treatment

Despite these complexities, genetic testing is becoming an essential tool for kidney disease specialists. The information it provides could help to diagnose and treat the disease earlier — well before the person progresses to kidney failure.

"Every year we have children who come in the door and go straight onto dialysis," says Quinlan. Dialysis — in which a person's blood is diverted through a machine that can do some of the work of the kidneys by removing waste products — is challenging for adults, but it is especially hard on children. If the disease is picked up earlier, before children reach the point of needing regular dialysis, other treatment and preventive measures can be used to slow down or even prevent deterioration in kidney function.

In Melbourne, Quinlan and her colleagues test any person suspected of having genetic kidney disease. Their testing programme started a few years ago for people showing symptoms of Alport syndrome, but has now expanded to include anyone with a red flag for a genetic underpinning of their disease, such as more than one person in a family with kidney problems.

The programme is funded to carry out an initial genetic analysis on the person with kidney disease, followed by two repeat analyses over their lifetime. It also entails testing members of their immediate family and their partner, and the provision of genetic testing and antenatal testing for those using fertility services to conceive, to avoid passing on the mutation.

The researchers are also trying to identify those at risk before people even notice symptoms, by trawling through electronic medical-record data for all children presenting at the hospital — even if just for a broken arm or other unrelated medical issue — to look for potential warning signs of kidney disease, such as blood in the urine.

"We're utilizing all of the data, merging it all together and trying to find markers for early-onset kidney disease, so that we can invite kids in to the nephrology service and offer them genomic testing," Quinlan says. This 'cold calling' approach is a very different model of care from the usual one, but Quinlan says it is already proving its worth.

"Every year we have children who come in the door and go straight onto dialysis."

"We've picked up a few kids with Alport syndrome that way, who had been to the hospital for an emergency-department admission years ago and had no concept that they were at risk of this disease and were not known to the kidney services," she says.

The advantage of early detection is that many of these children benefit significantly from early treatment with drugs such as angiotensin-converting enzyme, or ACE, inhibitors, angiotensin-2 receptor blockers or SGLT2 inhibitors, which can slow progression of the disease.

Genetic testing can also provide answers when there is no obvious other cause or risk factor for kidney disease, says Mallett. He's leading a programme that is using whole-genome sequencing to test children and young adults with unexplained kidney failure, and says the results so far are eye-opening. "The proportion of those patients where there was an answer to be found with genomic testing I think is paradigm changing," Mallett says. He anticipated a diagnostic rate for genetic disease of around 5%, but it has been several times higher than that.

Understanding the potential genetic underpinnings of CKD can significantly change an individual's treatment. For example, the standard treatment for primary focal segmental glomerulosclerosis, which is thought to be an autoimmune form of kidney disease that causes scar tissue to develop on tiny networks of blood vessels known as the glomeruli, is immunosuppression. But it's now thought that mutations in a *COL4A* gene cause similar scarring because of structural changes in the glomeruli. "If it's structure and you give immunosuppressive medications, all you do is give them a chance for more infections and cancers without benefiting," Parsa says. Testing for this genetic variant in people with scarring could avoid unnecessary immunosuppressive treatment.

Researchers are also interested in developing drugs to target the pathophysiological mechanisms of certain genetic kidney diseases, such as those associated with the gene *APOL1*.

This variant appears with a higher frequency among people from sub-Saharan Africa, because individuals who are carriers of the mutation are resistant to an infectious disease found in the region called trypanosomiasis, or sleeping sickness (A. Cooper *et al. eLife* **6**, e25461; 2017). APOL1 inhibitors could help to treat this particular form of the disease, and these potential drugs are already showing promise in clinical trials.

Mallett sees genetics as the next frontier of nephrology, and the ability to diagnose monogenic CKD is just the first chapter of that story. "Now we're entering into this phase where polygenic risk scores and polygenic contributors to disease — particularly kidney disease — is dawning," he says. He sees a future in which genomic testing will be deliverable in the clinic, "on an everyday basis, as part of standard of care".

For the 18-year-old whose disease had puzzled Mallett at the start of his career, understanding the genetics underlying the disease addressed the fears that the man and his brother had that they could pass it on to their future offspring. "By virtue of it being a mitochondrial disorder, then they would have confidence that the children of those two affected men would not inherit the condition," Mallet says. There isn't yet a treatment approach targeted to that variant, but knowing future generations were safe from it, "that meant so much to them".

Bianca Nogrady is a freelance science journalist based in Sydney, Australia.