THE LOST BOYS

A startling genetic breakthrough by a New Zealand scientist solves a tragic puzzle for one family and offers hope for the treatment of many congenital diseases. BY PAMELA STIRLING

There are some fates that once only the gods could predict. When Christopher, the first of June Miru's infant grandsons to die of tragic deformities, was born to her daughter Karen in 1988, "they said it was 'bad luck' and would never happen again in a million years", says Miru. That was in September of that year. By December, two more of her daughters – Shona and Phyllis – had also given birth to babies with the same deformities. One little boy, Joshua, was to live for an almost miraculous nine days; so weak that his cry was like a kitten's mewing. "He was the most beautiful little boy, they all were," says Miru.

Altogether in this family, seven baby boys with the syndrome have now died; most living for just a few hours after birth. "For it to happen a second time and then a third time and for it to keep on happening was just devastating, especially when you don't know what's going on," says Karen Tito, Christopher's mother.

Just weeks ago, on a wet Auckland Sunday, Miru and her family gathered at the cemetery to bury Ali Pomare, the last in this tragic line and so tiny that he never breathed. The sobs of the five-year-old saying goodbye to the second of his siblings "just broke my heart", says Miru. "You'd think we'd get used to it, but everyone was just bawling."

But at least this time they knew the reason why this child could not survive. And now they know that there is an accurate way of predicting whether it will happen again.

JANE LISSNER

From left, Shona Tito, Hemoata Tito with Che Clark-Miru, Karen Tito, Noki-Jane Miru with Zinnia Clark-Miru, June Miru and Michael Tito: they have lost seven baby boys as a result of a gene mutation.

Early last year, Professor Stephen Robertson, Chair of Child Health Research at the University of Otago, made a groundbreaking discovery: the cause of the syndrome affecting June Miru's family was a deadly mutation in a single gene called FLNA. It began with Miru and was passed on to her daughters. Each of those four daughters has now lost a baby, some of them two.

"Why did it start with me?" Miru asks Robertson, on the day we all meet at a West Auckland restaurant. "It was just a random hit," explains Robertson. "It happens because DNA needs to be copied for our genetic constitution to be transmitted, and as it's copied, mistakes get made. The environment damages our DNA. We all actually get around 100 DNA-based changes each generation. Most, of course, cause no harm. But not many people realise that one in every 40 children suffers some sort of birth abnormality. It's just that it's not always immediately evident to the onlooker – it might be a kidney problem, or a heart problem."

What's so significant about the revelation of the FLNA gene as the cause of June Miru's problem is that it could well prove to be one of the links that helps stop the heartache of congenital defects in many other families.

And for that we can he thankful for two things. The first is that June Miru, after the loss of her firstborn baby Wati, in 1963, did not give up hope. Wati, born two months premature, died of the deformities caused by the condition: "I wasn't even allowed to see that baby," says Miru, now 63. But she went on to produce four daughters – all carriers, despite the 50/50 odds that they would escape it – and a son who survived. "And that's why we've been able to study this family – you need a big family to study a condition like this," says Robertson. "You need to do a statistical analysis of the way certain genetic markers are carried down the generations, and whether those genetic markers and the path they take as they are transmitted corresponds with the path the disorder takes." But the chances of finding the cause of this particular disorder were staggeringly small: the human genetic code comprises 3000 million individual units, packaged into 23 chromosomes.

And so it was another stroke of luck that Stephen Robertson, now 37, learnt of the story of June Miru's family as a young practising paediatrician and became determined to hunt down the cause of their misery.

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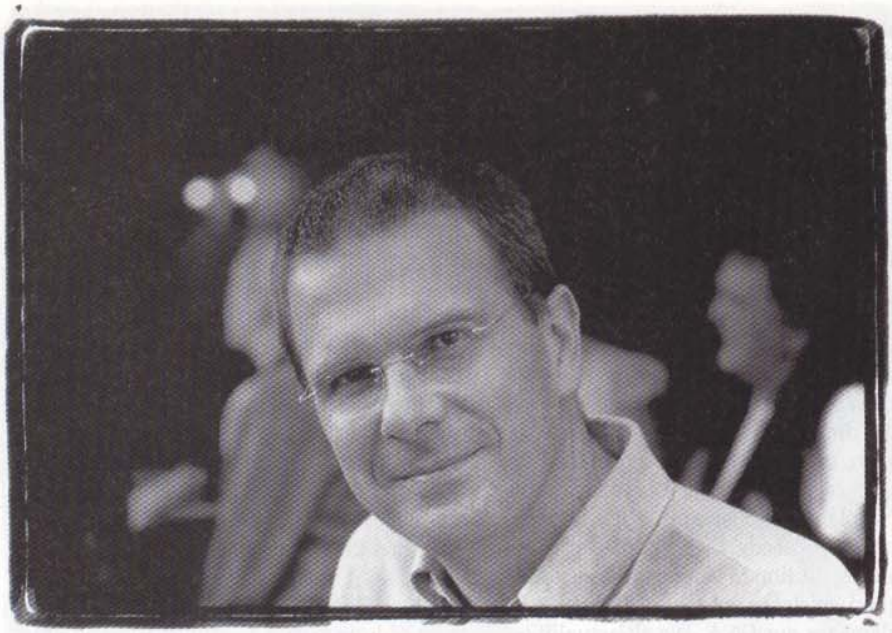
Robertson had graduated with distinction in 1990 from the Otago Medical School with the Alumnus Association Prize in Medicine for first place in his class and had also received the coveted Prince of Wales Prize for the most outstanding student completing an undergraduate degree at the university.

First, Robertson induced a friend at Oxford to begin studying this family. "A few years later, I went to join him," he says. With the help of Professor Andrew Wilkie, Nuffield Professor of Pathology at Oxford University, the approximate chromosome address of the faulty gene was tracked down. But the hunt



Professor Stephen Robertson: the hunt for the right gene proved "soul-destroying at times".

for the right gene was to prove "soul-destroying at times", says Robertson, who was by then a Nuffield Fellow at the Institute of Molecular Medicine at Oxford.

"Throughout the whole seven years of searching, Stephen has kept in touch with us," says Karen Tito, "letting us know how he was doing, even when he was getting nowhere. Even when he was in England, he would ring and track us down all over the country, and not just because he needed more blood. It has been very good for us as a family to know Steve. This was a very tender spot, none of us wanted to talk about it. It was a very freaky thing to have this keep happening in our family and not know why. We love Steve for the way he just kept going."

At Oxford, Robertson was able to locate 50 other families from 15 different countries – all unrelated to the New Zealand family – who had the same or a similar condition. Robertson was discovering that "there is a huge spectrum of severity within these disorders, from mild to fatal".

"What fooled us and threw me off the trail of this particular gene originally was that it had already been implicated in causing a form of epilepsy in otherwise normal female individuals," he says. "We didn't look at this gene for a long, long time because we thought that mutations in it just caused this epilepsy syndrome. There were no similarities between individuals with this seizure disorder and the malformations that I was studying. We thought if this gene causes epilepsy, then it's not going to cause the syndrome suffered by June's family. The penny finally dropped in February last year. I began to look at it and there were all the answers."

It has created "quite a stir", he confirms, to discover that altered forms of a protein, filamin A, for which the gene FLNA carries the code for production, underlie birth defects in children. This protein, which is part of the "scaffolding" of cells, turns out to be critical for the development of embryos. "These scaffolding proteins haven't been implicated in that side of biology before," says Robertson. "That was a definite surprise."

Robertson has now discovered 17 different "misspellings", or mutations as they are technically termed, within the 8500 DNA letters that comprise the FLNA gene. In the case of affected male babies in June Miru's family, the defects are always fatal. Christopher, says his mother Karen, was "born with organs not properly formed: his stomach looked like a transparent dome through which you could see the organs inside. His fingers and toes were twisted. His eyes were further apart than normal and he was also born with cleft palate." Affected male babies in this family have abnormalities of the skeleton, heart, kidneys and intestines.

Isolating the gene responsible for such deformity in an infant is such a significant scientific breakthrough that the results were featured in the April issue of the prestigious journal *Nature Genetics*. Because this is the gene responsible for a form of epilepsy, as well as a wide spectrum of congenital malformations, the indications are strong that the same gene might be the culprit in other childhood diseases.

"I'm now looking very broadly at more genes to see what other diseases they might be responsible for," reports Robertson. This research could make a big difference to lives and improve the quality of many children's existences. "This is an exciting moment," he says.

Already, Robertson is receiving DNA samples from affected families from many specialists around the world. "It is a real coup for him to be identified as the world expert in this field," says Child Health Research Foundation CEO Kaye Parker.

After finishing his fellowship at Oxford, Robertson has come home to head the $4 million Child Health Research Foundation Clinical Genetics Research Unit in Dunedin. About $500,000 of the foundation's funding comes from fundraising efforts by Cure Kids in the Queenstown downhill endurance ski race (July 24-29, see www.curekids.org.nz), the HP 50K of Coronet. With Robertson's appointment – hailed by the foundation's chairman as "the start of a major new era in research into child illness" – there are hopes of offshore funds. The university has already invested in a WAVE machine, a state-of-the-art automated system of rapidly and accurately identifying disease-causing mutations within DNA. Robertson previously did this painstaking task manually.

IN JUNE MIRU'S CASE, her surviving son is unaffected by the condition that Robertson has been researching, as are her three living grandsons, including Karen Tito's son Michael, 17. Michael's brother, his uncle and six of his cousins have all died of the condition, but he was born free of it. On the day we all meet, his grandmother again asks the professor for the assurance that Michael has already been given, but which she scarcely believes. "Michael's children will be all right?" "Michael doesn't have it and neither will his descendants," confirms Robertson.

Miru's granddaughters will now be able to decide, when they're old enough, whether they want to be tested to see if they are carriers. If they are carriers, there is a 50-50 chance that any male baby they conceive will have the condition, and there's a similar risk that they will pass it on to a daughter. One of Miru's little granddaughters is already a

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JANE USSHER

confirmed carrier. She was born with normal intelligence, but with a "very flimsy and very wavy" cervical spine, a cleft palate, a very narrow airway, chronic asthma and deafness – all caused by the condition. "She's very special," says Miru. She, too, has a 50-50 chance of having a child with this genetic condition. It is mostly males who suffer the deformities; this grandchild is the first female in the family to have symptoms of the condition and in her they are milder than in males. Only women pass on the mutations.

And no, the FLNA mutation is unlikely ever to be treatable by gene therapy in the womb, says Robertson. "The organs in a baby begin to form very early on after conception – the heart forms at four weeks, the skeleton from around six weeks after conception – and that's when this gene has its effect," says Robertson. "A woman scarcely knows she is pregnant before all of this has happened."

If they could afford it – and they can't – the women in this family could have IVF and have the embryos tested for the gene before implantation. Pre-implantation genetic diagnosis (PGD) can prevent more than 100 genetic conditions, ranging from Down's Syndrome to Huntington's disease, haemophilia and cystic fibrosis. The procedure sparked headlines last year when Chicago geneticist Yury Verlinsky helped a 30-year-old woman give birth to a baby free of her family's curse of early onset Alzheimer's disease. The opportunity for PGD exists in Australia, but not here.

But if any of June Miru's daughters falls pregnant naturally, there is the option of gene testing and termination. It's a heart-wrenching decision – the family has already faced this issue – but any baby boy with the syndrome afflicting Miru's family will die anyway: it's just a matter of when. Two of her daughters say they would have a termination. Another has already had her tubes tied because, after losing two babies to the condition, the prospect of another pregnancy is just too frightening. But one daughter, Shona, who has also lost two babies – one was not officially diagnosed with the family's syndrome and in fact takes the family's tally of lost boys to eight – says that, if she became pregnant, "I would carry on to the bitter end."

Yet, unravelling the genetic code creates a whole new tangle of ethical dilemmas. What if the unborn baby was revealed to be a girl, with lesser symptoms of the condition? What level of disability is too great for families to face? It would be hard to argue that the world is not a better place for Helen Keller having been born blind and deaf, or for Beethoven's birth, despite his later deafness.

As they sit around the kitchen table, still tearful the day after they have buried little Ali, Miru's daughters Karen, Shona and Noki-Jane know exactly how hard any future decisions will be. And soon the dilemmas may not just be theirs. Currently, most reproductive centres around the world offer PGD only for diseases that are either fatal or carry severe morbidity for the babies – and for which prenatal diagnosis is currently offered, anyway. It often saves an abortion later in the pregnancy. But what if genetic testing enabled PGD screening for alcoholism or schizophrenia or heart disease?

"I don't know any geneticist who has the agenda of cleaning up the world of disability," says Robertson. "This is not eugenics. What we're actually about is helping people understand and live with disability as best they can, and part of that's through giving information about what causes it.

"What this research did for us is take away that overwhelming guilt, when you hold your baby and think, 'What did I do wrong?'" says Karen Tito. "And it gave us choices."

But there is one last thing about which Miru needs to quiz Robertson: "Tell me just how accurate your test is. What if it showed a baby in the womb had the condition and it was terminated, but in fact that baby could have been born with nothing wrong? I just worry about it because we were told once that the odds were a million to one, and they weren't. I'm not getting at you."

"I know you're not, June," says Robertson. "This is a very important point you raise. This test is extremely accurate; nothing in genetics gets more precise. This is a straight 'Yes' or 'No' test; so accurate I'd put it at a thousand to one."

Miru nods. Now she understands. Karen puts her arm round her. "You look knackered," she says, gently. "It's taken all this time for it to really hit me," agrees her mother. For someone who can relate her whakapapa back many generations and who wonders whether the lineage will continue, the stakes here are extremely high. Miru's grandson Michael, for example, having grown up seeing so many little white coffins, so many tears, could well have decided without Robertson's research not to have any children. But Michael leans confidently on the kitchen doorframe a few weeks later – it is a day or so after Ali's burial – and assures his grandmother and mother that he knows he was born under a lucky star. And there in his eyes is a tiny but unmistakable glint. "Don't worry, Mum," he says, "one day I'm going to have lots of children." ■