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What Does the Future Hold? Solving the Mysteries of Rare Diseases

Next-generation gene sequencing can help spare parents years – sometime decades – of not knowing what's wrong and how to best care for their children.

AT A GLANCE

Who: Dr. Kym Boycott, Children's Hospital of Eastern Ontario Research Institute

Issue: There are an estimated 7,000 rare diseases, most of which affect children and only half of which have an identified genetic origin – leaving about 3,500 identifiable only by the symptoms they cause. Families of children with a suspected rare disease are left in the dark, often waiting years to get a definitive diagnosis and, with it, appropriate care.

Project: Over the past two years, Dr. Boycott, a clinician-researcher who specializes in the genetic origins of neurological disorders, has led a consortium called FORGE Canada (Finding of Rare Disease Genes in Canada) to study the genetic causes of 200 rare diseases. FORGE solicited proposals from clinicians across the country to identify the specific rare diseases that they would study. The consortium brings together 150 clinicians and scientists working at 21 centres across Canada and has enlisted the help of geneticists in 17 countries.

Research Evidence: Using high-throughput, next-generation sequencing, FORGE has already found the disease-causing gene mutations for more than 100 rare diseases. The scientists expect they will have identified the genetic origins of 130 – or about two-thirds of these diseases – by the end of the year.

Evidence in Action: More than 500 families have received diagnoses for their children's conditions since FORGE set to work in April of 2011. This has saved families from years of not knowing what was wrong with their child and spared the children from undergoing (and the health care system from providing) needless tests and procedures. Children get care tailored to reduce or prevent complications, even if there is no cure for their disease.

Sources: McMillan, Hugh, et al., "Specific combination of compound heterozygous mutations in 17β-hydroxysteroid dehydrogenase type 4 (HSD17B4) defines a new subtype of D-bifunctional protein deficiency," *Journal of Rare Diseases* 7, 90 (2012): doi:10.1186/1750-1172-7-90. Interviews with Dr. Kym Boycott. FORGE Canada website.

Kathy O'Connor could tell something was seriously wrong with her two sons. Instead of growing stronger, they were regressing.

At 11 years old, the once robust T.J., who played hockey and soccer, was having difficulty walking in a straight line and started bumping into walls. His speech slowed and his fine motor skills deteriorated. Casey, about two-and-a-half years younger, experienced similar difficulties – although not as pronounced.

"I guess 'a nightmare' is the best description," says Ms. O'Connor, a nurse practitioner who lives in Pembroke, Ontario.

Video with Dr. Boycott

- Watch the video
- Read the transcript

What followed was four years of tests and doctors' visits as the family attempted to find the cause behind T.J.'s and Casey's declining health and wellbeing. The boys underwent multiple biopsies and MRIs, CT scans and blood tests. Neurologists and cardiologists, urologists and endocrinologists studied the boys but no one could find an answer.

"The not knowing – you can only imagine," says Dr. Kym Boycott, a clinician-researcher at the Children's Hospital of Eastern Ontario in Ottawa, who assessed the O'Connor boys. "It is one of the most difficult things in my job: to watch a beautiful child go backwards, to regress, and not know why."

Until recently, there was not much Dr. Boycott could do. Her specialty is neurogenetics, which involves studying the genetic factors that contribute to the development of neurological disorders. "When a child who had some undiagnosed degenerative condition came to my clinic and they had all kinds of tests and we still didn't know what was going on, we'd be stuck. We would have to tell the parents, 'We don't have an explanation and we don't know what's going to happen.'"

However, the use of next-generation gene sequencing in tracing the genetic origins of rare diseases has "revolutionized the way we look after these kids," says Dr. Boycott.

She leads FORGE Canada, a consortium comprised of 150 clinicians and scientists – most of them clinical geneticists – studying the gene mutations behind 200 rare diseases. The FORGE team chose the list of diseases following a national request for proposals to suggest targets for study. Up and running since 2011, FORGE has used next-generation sequencing to crack the mysteries behind more than 100 rare conditions and its investigators are confident they will unravel many more.

Next-generation sequencing: much faster, far less expensive

Gene sequencing used to be a slow, laborious and costly enterprise. The most popular method, Sanger Sequencing, has been in use since 1977 and, in essence, involves studying the DNA sequence of one section of a single gene at a time. If you were looking for a needle in the haystack, this would be like searching the pile one strand of hay at a time. With next-generation sequencing, all 22,000 genes in the human genome can be sequenced in parallel. The process takes two to three weeks and costs about the same as sequencing a single gene the old way – about $1,100. While the use of next-generation sequencing to track the genetic roots of rare diseases is becoming more common, Dr. Boycott was a very early adopter of the technology – thanks to funding from the Canadian Institutes of Health Research (CIHR): "The first description

of this being applied to rare diseases was in 2009. CIHR jumped on this early on – because we started with this in 2010 when we had our first workshop. That's how early we got in the game."

What is a rare disease?

It is estimated that there are as many as 7,000 rare diseases[1] (sometimes called orphan diseases). Many are genetic in nature with the symptoms first appearing in childhood. In fact, about 75% of rare diseases affect children and almost one-third of children with rare diseases die before their fifth birthday.[2] Definitions of what constitutes a rare disease vary around the world. In the United States, the National Institutes of Health define a rare disease as one affecting fewer than 200,000 Americans – roughly the equivalent to one in 1,500.[3] The European Commission suggests that rare diseases are those that affect fewer than one in 2,000 people.[4]

One of the major mysteries solved by Dr. Boycott and FORGE involved T.J. and Casey O'Connor. The boys have a rare version of a disease called D-bifunctional protein (DBP) deficiency, which is triggered by a genetic mutation that inhibits the function of an enzyme. The mutation causes damage to the nervous system, hearing, vision and balance. Dr. Boycott co-authored a paper on the discovery in 2012.[5]

The DBP revelation is the kind of discovery that can vastly improve a child's life – even if there is no treatment or cure available. "If you're a child with developmental delay in the public school system, you don't have the same access to services that you would if you have an actual diagnosis," says Dr. Boycott. "As well, they may be at risk for some long-term health complications that we can screen for and possibly impact. We can improve outcomes this way."

Beyond providing peace of mind, there are considerable cost savings to be realized in quickly and efficiently diagnosing rare diseases. In a 2011 *Ottawa Citizen* article, Dr. Boycott estimated she had spent about $20,000 in health care costs on various tests for the O'Connor brothers before next-generation sequencing technology came into use as a way to track rare diseases. The DNA scan that identified the deviant gene cost about $1,100. Multiply those savings by the thousands of patients Canada's geneticists see every year – FORGE investigators estimate genetic disorders affect the lives of about 500,000 children in Canada[6] – and the health care costs saved could amount to billions of dollars.

Evidence in Action: Cost savings resulting from a firm diagnosis of rare diseases

FORGE's work has given conclusive diagnoses to more than 500 families with children who have rare diseases. A proper diagnosis helps doctors plan appropriate care and eliminates the need for further time and expense spent on diagnostics. In the case of T.J. and Casey O'Connor, health care system costs for inconclusive tests amounted to $20,000. The DNA scan that provided a firm diagnosis cost just $1,100.

While knowing the genetic root of a disease does not mean treating it or curing it – genes can't simply be repaired or even tweaked – it may point to a possible therapy.

"We've had a couple of the 100 disorders solved so far where there's an obvious treatment that might be considered," says Dr. Boycott. "One was a vitamin deficiency that caused a neuropathy. Another

was a manganese deficiency – the children can't absorb manganese in their diet, which might indicate that supplemental manganese could have a positive effect. These, of course, would require clinical trials, which is beyond the current scope of FORGE, but these opportunities for possible straightforward treatments need to be pursued for these patients."

The next best scenario, she says, is the possibility of repurposing existing pharmaceutical treatments for rare diseases. "For example, if they have over-activation of a pathway and there are inhibitors that have been developed by drug companies, often for cancer treatments, these could be possible routes to treat some of these diseases," says Dr. Boycott. That option is far more realistic than designing new drugs to treat rare diseases, which can take decades and cost tens of millions of dollars.

In most cases, parents are just happy to know what is wrong. The discovery came as a relief to the O'Connor family – even though there is no treatment or cure for DBP. "We definitely wanted a diagnosis. Otherwise, it's hard to look ahead," says Ms. O'Connor.

The O'Connors' reaction is typical, says Dr. Boycott. "Even if their child has something terrible, the parents want to know. They want a name for it. They want to know, 'Are there any other kids like this in the world that we can learn from? What sorts of things have helped in the past with the kids' day-to-day lives to make things as good as possible? And what does the future hold?'"

FORGE-ing forward

While the FORGE consortium has three lead institutions – the University of Ottawa, the University of British Columbia, and the CHU Sainte-Justine research centre – it brings together doctors from genetics centres across Canada, internationally-recognized Canadian scientists with expertise in finding genes, and teams from the three Genome Canada Science and Technology Innovation Centres in Toronto, Montreal and Vancouver.[7]

For More Information:

- FORGE consortium website
- Orphanet Canada website
- Canadian Organization for Rare Disorders website
- National Institutes of Health Office of Rare Diseases Research
- Video with Dr. Boycott

1. Orphanet Canada. *About Rare Diseases*.
2. European Society of Paediatric Oncology (SIOPE). *Rare Diseases: Did you know?*
3. National Institutes of Health, Office of Rare Diseases Research. *Frequently Asked Questions*.
4. European Commission. *Useful Information on Rare Diseases from an EU Perspective*. 2004 [PDF (112 KB) - external link].
5. McMillan, Hugh, et al., "Specific combination of compound heterozygous mutations in 17β-hydroxysteroid dehydrogenase type 4 (HSD17B4) defines a new subtype of D-bifunctional protein deficiency," *Journal of Rare Diseases* 7, 90 (2012): doi:10.1186/1750-1172-7-90.
6. Genome British Columbia. *Finding of Rare Disease Genes in Canada (FORGE)*.
7. Ibid.

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