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Canadian team finds root causes for 146 rare childhood diseases

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The baby was born in 2008 with an unusually small head, dozens of tiny red birthmarks and uncontrollable seizures.

No one had seen anything like it at the Children's Hospital of Eastern Ontario, so researchers there documented the baby's symptoms and dubbed the condition "microcephaly-capillary malformation syndrome."

Now, by comparing the baby's DNA with that obtained from a handful of similar cases worldwide, Kym Boycott, a clinical geneticist at the Ottawa research hospital, and her colleagues have pinpointed the single gene mutation responsible – and they have done the same for 145 other rare childhood diseases.

"I think the biggest impact that will come from this is in our ability to change the way we care for patients," Dr. Boycott said.

The avalanche of new discoveries, reported Thursday in the American Journal of Human Genetics, is the fruit of a co-ordinated nationwide study called FORGE (Finding of Rare Disease Genes in Canada).

Researchers and clinicians are praising the ground-breaking effort, saying it will enable rapid diagnoses, guide treatment and in some cases point the way to future therapies for children living with the burden of little-known but often severely disabling genetic deficits.

"Even if we don't have a treatment, having a diagnosis is invaluable to patients and their families," said Ada Hamosh, clinical director of the McKusick-Nathans Institute of Genetic Medicine at Johns Hopkins University in Baltimore, who was not involved in the study.

Researchers estimate there could be as many as 7,000 rare diseases. Such diseases have received little attention until now because they typically occur in fewer than one in 2,000 people.

Many of the disorders remain undocumented, which means those who are afflicted by them have had little hope of knowing the cause of their disorder, let alone of finding an effective treatment.

Starting in 2011, the FORGE collaboration was among the first to leverage new high-speed DNA-sequencing technologies to tackle the rare disease conundrum.

"FORGE Canada and Kym Boycott were ahead of the world and have continued to lead the world in data sharing and bringing tools to understand the causes of rare disorders," Dr. Hamosh said.

In setting up the project, Dr. Boycott and her colleagues solicited clinicians across the country to submit information about rare cases they had encountered. Out of 371 submissions, they identified 264 children or young adults who from birth exhibited the hallmarks of a rare genetic disorder.

Some of the disorders only affect a single organ, such as eyes, ears or heart. Others are more broadly debilitating, include severe problems with brain development and can lead to early death.

"You get the whole spectrum," Dr. Boycott said.

To identify a cause for each disorder, the FORGE team paired their Canadian cases with at least one unrelated case of the same syndrome elsewhere in the world or, in some cases, with an unaffected sibling.

They then rapid-sequenced the whole exomes of all those individuals, along with parents and sometimes other family members when necessary. The exome is the fraction of the human genome that codes for all the various proteins in the human body.

By comparing exomes, the team was able to narrow down which of the thousands of possible human genes might be implicated in a given disorder. While this approach is not workable for complex diseases like cancer, which involve many genes, it is remarkably effective for disorders that result from a single mutation in the exome.

Of the the 146 genes that were identified by FORGE, 67 had never been linked to a disease before.

"That's explosive," Dr. Hamosh said. "The impact of a single disease-gene relationship is wide open for research and immediately clinically applicable."

Dr. Boycott, who is among those now involved in an international version of FORGE, said that the ability of the Canadian clinical community to work together on identifying rare diseases has attracted the attention of other nations where researchers are less collaborative.

"All clinicians are dedicated to patient care but I think in Canada we just have less ego about it so that we can get things done at a rate that other countries cannot," Dr. Boycott said.

Phil Hieter, a professor of medical genetics at the University of British Columbia, said that the discovery of rare disease genes by FORGE will allow researchers who study the counterparts of those genes in model organisms such as yeast or fruit flies to follow up and try to find out how a loss of function triggers disease.

"Knowing what a gene does, how it's regulated ... That's where the answers lie," Dr. Hieter said.

Dr. Hieter added that the transformative impact of sequencing technology suggests that by 2020 scientists will have discovered most if not all of the human genetic variants that can cause disease. By then whole exome or whole genome sequencing could be a go-to first step for doctors with patients or newborns showing signs of a disorder, or it could be in common use for prenatal screening.

There are myriad of ethical considerations that must be taken on board in such circumstances, experts say, and health care providers have not yet caught up with the changing diagnostic landscape.

"One of the challenges of this technology is that with the wanted information comes the unwanted information," said Sarah Bowdin, a staff physician in clinicial and metabolic genetics at the Hospital for Sick Children in Toronto. "We need to work out who we offer this technology to and when."

Dr. Bowdin was one of the organizers of a think thank held in Toronto this week where those in attendance grappled with the implications of rapid, all-encompassing genetic diagnoses

The group expects to publish its recommendations later this fall.

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