Unveiling the bottlenecks to discovering the root causes of rare genetic diseases

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"We need new strategies to solve the unsolved," Dr. Boycott said. "Diagnosing the genes responsible for rare genetic diseases is a crucial first step towards informed patient care, giving patients a better understanding of what is causing their mysterious symptoms and helping doctors to better manage complications. We've made tremendous progress in linking rare genetic diseases to their causative biological pathways. However, the lack of data-sharing infrastructure is siloing data and hindering further discoveries. This paper for the first time sets out these pinch points so that they can be considered and addressed by the genetics community."

The paper also describes the increasing challenge of discovering novel disease mechanisms and confirming their links to rare diseases. The arrival of genome-wide sequencing in 2010 resulted in a boom in the number of disease genes identified but the rate of new discoveries has plateaued or decreased in recent years. Whole Exome Sequencing, for example, allowed researchers to zone in on the exome, the portion of the genome which encodes for proteins and where 85% of mutations originate. However, as many 'straightforward' genetic links have been identified, rare diseases are getting rarer and more difficult to solve.

Taila Hartley, operations director of Care4Rare based at CHEO, said some rare genetic diseases are one in a million rather than one in 300,000. Being able to confirm a genetic cause with a second patient from another country that may be recorded in a database makes a huge difference in building evidence.

"With whole-exome sequencing, there was a huge boom in new genetic discoveries. We thought this was going to continue but what we've realized now is we're experiencing a plateau or even actually a decrease in the number of genes that are being identified each year. And it's because we didn't..."
realize the international scale of data-sharing that
would be necessary to solve these ultra-rare
diseases,” Ms. Hartley said.

Dr. Boycott, co-founder of Care4Rare, a nation-
wide network of doctors, scientists and clinical
researchers dedicated to improving the diagnosis
and treatment of rare diseases, also helped
establish the Matchmaker Exchange with University
of Toronto scientist Dr. Michael Brudno. The
Matchmaker Exchange is a data platform that
enables sharing of rare disease patient clinical and
genomic information from around the world.

Key facts:

- 50% of rare genetic diseases are
  undiagnosed
- International databases have documented
  around 260 new rare genetic diseases each
  year from 2012-2015
- It takes two to three years to find another
  unrelated individual with a mutation in the
  same gene after publication of single patient
  / family
- Around 30% of clinical diagnostic success
  depends on recent progress in the
  discovery of the genes underlying disease

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