Mystery of rare diseases: Why diagnoses remain elusive

The experiences of Karen Park and Peter Loretzen are every parent's nightmare. Moments after their son, Milo, was born, he was whisked away to a neonatal intensive care unit. The newborn was severely jaundiced and had low blood sugar. And, soon, doctors discovered a hole in his heart. But repeated tests failed to answer a seemingly simple question: Why was their son so sick?

Five years later, the Loretzens may finally have an answer. Geneticists believe his health problems stem from the mutation of a single gene, KDM1A, which plays a key role in the activity of other genes.

Milo's condition falls into a broad category of rare genetic diseases known as Mendelian disorders – which are caused by a mutation on a single gene. Most human diseases involve a complicated cocktail of factors–usually the interaction of multiple mutations on more than one gene along with environmental factors. There are between 20 million and 30 million people in the U.S. affected by these disorders, according to the National Institutes of Health (NIH).

Such rare diseases are defined by the Orphan Drug Act of 1983 as conditions that affect fewer than 200,000 people. Among the most well-known of these disorders is Huntington's disease–an inherited disease that causes the progressive breakdown of nerve cells in the brain. Unlike Milo's disorder, Huntington's is easy to diagnose. If someone inherits the mutation that causes the disease, she has a 100 percent chance of getting the disease.

More information:

- Genetics Education Center, University of Kansas
- Specific Genetic Disorders, National Human Genome Research Institute
- Genetic and Rare Diseases Information Center
- Global Genes

Most rare inherited diseases aren't so predictable. The mutation that causes cystic fibrosis, for example, can exist without causing the disease. Scientists believe that environmental factors, gene-gene interactions or how genes are programmed to express can interfere with the mutation and keep it from causing disease. Geneticists call this "penetrance"–the proportion of individuals carrying a particular variant of a gene (allele or genotype) that also expresses an associated trait (phenotype). In medical genetics, the penetrance of a disease-causing mutation is the proportion of individuals with the mutation who exhibit clinical symptoms.

But Milo's condition, and that of many people with extremely rare disorders was not inherited, as neither of his parents carry the mutation. Instead, his disease was caused by a spontaneous mutation–something that can be caused by several factors, including errors in DNA replication. That presents unique problems to doctors and researchers trying to diagnose rare disorders.

Small patient pool

Researchers are still learning about spontaneous mutations and how they relate to diseases. Among the discoveries: These mutations are not uncommon, but they don't typically cause disorders, said Michelle Snyder, a genetic counselor for the NIH's Genetic and Rare Diseases Information Center.

One of the things working against Milo is the fact that he is one of only three people in the world known to have been diagnosed with the same mutation. The symptoms included "low muscle tone and a body that lacked strength, making him slow to lift his head or push up off his stomach; delays in mimicking people and expressing himself," according to a story by National Public Radio.

Traditionally, scientists researching diseases rely on large numbers of people with similar symptoms to create large databases. Researchers use that data to look for shared genetic mutations. But since rare disease populations are so small, this method isn't as effective.

Recent advances in genetic research techniques – exome sequencing, in particular – are showing promise for researchers studying such rare conditions. The exome is a small subset of our DNA (about 1 percent) that code how proteins function in our bodies. This offers an advantage for research into rare diseases. The cost of exome sequencing is considerably lower than the cost of whole genome sequencing, making it possible for researchers to assemble large exome databases for study.

But there are problems. The first is that many of these databases are built using data collected from people of European descent, resulting in a lack of human genetic diversity. There also are issues with a lack of openness, with databases often kept private, decreasing the opportunity to learn from those larger exome pools.

This latter weakness was illustrated by the Exome Aggregation Consortium (ExAC), in an August 2016 study published in Nature. Researchers looked at individual exome databases and collected 192 genetic variants that had been reported as potentially disease-causing. But when they expanded into a larger data set with a more diverse population, they found that only nine variants "had sufficient data to support disease association."

The consortium, which has published its own database of some 60,000 people, is pushing for greater sharing of data to improve our ability to diagnose rare diseases.

But even as we get better at identifying these rare disorders, that does little to help people like Milo and his parents, for whom diagnosis is simply one more step down a painful path.

Research funding gaps

There are approximately 7,000 identified rare diseases. And considering the relatively small number of people afflicted by them, it's not surprising that they don't receive priority when it comes to research funding. In general, large funding bodies (such as the NIH) are more likely to support research into disorders – cancer, heart disease, etc. – that affect large segments of the population.

While many would argue that funding should be allocated in ways that will affect as many people as possible, some scientists argue that there are hidden benefits associated with research into rare diseases. Jeremy Reid, a finalist in the Orphanet Journal of Rare Diseases essay contest, and a current clinical medical student at the University of Birmingham (UK), wrote:

> *…a rare disease with an underlying monogenic pathology indicates that the genetic variant in question is important enough to cause sufficient physiological disruption to cause clinical disease, but that it is compatible with life, therefore essentially self-selecting genes worthy of study.*

Essentially, Reid says that although everyone wouldn't directly benefit from the study of obscure gene mutations, studying them increases our knowledge of how our genes function normally. For example, Reid mentions in his essay a very rare disorder called congenital leptin deficiency. People who have this disorder are unable to produce the adipokine leptin–a protein that helps regulate hunger–because of gene mutations on what's known as the ob gene.

Researchers working on the ob gene and related genes to find a treatment for congenital leptin deficiency also learned a great deal about how genetics affects weight gain and obesity. And while it hasn't led to any effective weight loss treatments, it's given researchers hope of discovering one.

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