Expert discusses RNA's role in diagnosing rare diseases

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An individual's genetic makeup, or genome, can reveal important and intimate details of his or her biology. Now, scientists are showing that RNA, the lesser-known molecular cousin of DNA, is powerful in its own right and can provide insights into rare human diseases that DNA cannot. Stephen Montgomery, Ph.D., associate professor of pathology and of genetics at the School of Medicine, is among the scientists harnessing RNA to identify the cause of rare diseases that have eluded mainstream

medicine.

In a study published June 3 in *Nature Medicine*, Montgomery and his colleagues describe how RNA sequencing, or transcriptomics, helps pin down the genetic roots of rare diseases. While DNA sequencing of the genome can reveal certain mutations or gene abnormalities present from birth, RNA transcriptomes show what happens when those genes are turned on, or expressed, as well as how our environment can sway the activation and level of expression of our genes.

Science writer Hanae Armitage spoke with Montgomery about his work in transcriptomics, its role in disease diagnosis and some of the rare diseases he and his team were able to identify using insights from RNA.

1. What is transcriptomics?

Montgomery: We're probably all aware that DNA makes up all of our genes. But for these genes to actually have an effect, their genetic code is used to make molecules that are useful in the body, such as a proteins. During this process, there's an intermediate step where the DNA of a gene is expressed, and it gets transformed into molecules known as messenger RNA. This mRNA clues us into which genes are active in an individual. Collected as a whole, these mRNA molecules form the transcriptome. It allows us to study the activity of all the genes in a particular cell, or in a particular biological state. We can, for instance, use a sample of an individual's blood to determine which genes are active at any given time, like when he or she is experiencing a strange medical symptom. But unlike DNA, which is more like a static blueprint of a person's biology, mRNA is dynamic. Depending on what people do—smoke, eat fatty foods, run, whatever—it can change how genes are expressed, and we can use those expression patterns to decipher all sorts of different health risks or exposures.

2. How do you use transcriptomics to zero in on the cause of difficult-to-diagnose diseases?

Montgomery: Right now with genome sequencing we can identify hiccups in the DNA, such as mutations, which are more broadly known as gene variants. But we all have a variety of these gene variants, and not all of them are bad; some don't have any effect. With transcriptome sequencing, we're able to see if those genes, variants and all, are functioning normally. Sometimes a gene that looks fine on the level of its DNA is actually malfunctioning, producing too much or too little protein, for instance. And we can detect this from the transcriptome.

So when evaluating a patient's transcriptome, the two things that we've focused on have been the level of gene expression and how that level compares to levels in healthy individuals, as well as something called splicing, which is how the transcript—the raw sequence of RNA after transcription—is pieced together to make the correct sequence of mRNA.

3. Can you give me an example of a case where transcriptomics helped identify the cause of a rare disease?

Montgomery: We had a female who was experiencing problems with normal development. After developing normally until she was 18 months, she started having problems with head control and speech; at 21 months, she started developing tremors; and at 22 months, seizures. So we did DNA sequencing and we found about 110 different genes that could have been causing the problem. But by adding information from her transcriptome, we were ultimately able to home in on one specific gene because we saw a particular abnormality in the mRNA. The abnormality we found reflected knowledge from the literature about

aberrant mRNA patterns that can lead to symptoms similar to hers. So using the transcriptome allowed us to narrow down a very large number of candidate genes to one, which gave us some real traction on this case. Our hope is that in the future, we'll be able to use this information in developing new approaches for gene therapy as that field continues to advance.

4. How often do rare disease diagnoses benefit from transcriptome data?

Montgomery: With genome sequencing, we can find promising gene candidates for people who come in with an undiagnosed rare diseases 30% to 50% of the time. After that, there's a diagnostic maze of different things that an individual might have to undergo to figure out what's happening. There might be an environmental factor at play that's impacting their illness. Or perhaps there are multiple genes involved in their disease. These individuals are faced with finding the next step of disease interpretation. So in this study, we asked, "If we used transcriptome sequencing and applied it across a really broad range of disorders, how many people could we help find a diagnosis or more specific information about what's causing their disorder?" We found that for an additional 8 percent of patients, we could find the cause of their illness, and for another 17 percent, we were able to narrow down the candidate genes to understand what's behind their disease. So overall, it's about a quarter of the cases that we're getting improved traction on, in terms of getting closer to a diagnosis. We think this is only the lower bound on what is possible.

5. How do you see this approach fitting into health care?

Montgomery: Scientists in this field are really trying to think about how

we can create and use technologies that have the broadest possible human impact and are not just for a select few individuals. It's true that some sequencing technology is still very expensive, but we've seen dramatic drops in the cost of genome sequencing over the last 20 years, particularly in the last decade. And to get individual transcriptomes sequenced now is on the order of a couple hundred dollars. My expectation is that these approaches will continue to get cheaper and more accessible, especially as researchers and doctors continue to demonstrate the value and utility of these approaches in the clinic.

In addition, I think the public will become more accustomed to not only understanding their genome and DNA variants, but also to the fact that there's valuable information in the functional outputs of their genome—such as mRNA and proteins. This can provide really detailed information about the environments they're living in, the aging process, how they might react to certain drugs, all sorts of things that we just don't have good tests for right now. I think in the future, people will get their transcript sequenced multiple times throughout their life, just as they might have their blood cell counts measured at a clinical visit. I don't think it's too far of a stretch to imagine that, down the line, doctors will be able to access transcriptome profiles of their patients more routinely to better inform care.

More information: Identification of rare-disease genes using blood transcriptome sequencing and large control cohorts, *Nature Medicine* (2019). DOI: 10.1038/s41591-019-0457-8

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