FACING VARIANTS OF UNCERTAIN SIGNIFICANCE WHEN CONDUCTING GENETIC TESTING/WHOLE GENOME SEQUENCING

When a patient's DNA is tested, it must be decided if gene variants are responsible for the patient's disease. "In many cases strong evidence is found," says Stephan L. Zuchner, MD, PhD, professor and chair, Department of Human Genetics at the University of Miami Health System. "In other cases, it's quite clear that a variant is benign and not related to the disorder."

However, with current genetic testing methods, often more than 100 genes are examined at once and there's a good chance you will also find variants where a decision can't be made based on the current state of knowledge. This is known as a variant of uncertain significance (VUS). "It's a situation where you are really hard-pressed to make a decision on whether it is a completely benign variant versus it is clearly causing disease," he says.

VUS has become a major issue for clinicians because the more genes are tested on a regular basis, the more VUSs are found. "In the absence of a clear pathogenic change in a person, you have to revert," Dr. Zuchner says. "It is very unfortunate when we get a diagnostic report back and the physician who takes care of this patient is not in a position to rule out that this has a genetic cause, despite the extensive testing. A number of these VUSs are pathogenic, but we can't say for certain."

There is a set of rules that is used by all major clinical genetic laboratories for interpreting DNA variants. An advance over the last decade is that there is a large collection of population normative data, which has been made public through various databases. The most famous one is called the Genome Aggregation Database (gnomAD). "With aggregated data from several hundred thousand individuals available, the interpretation of genetic test from patients with neuromuscular disease has become easier," Dr. Zuchner says.

ClinGen, a National Institutes of Health (NIH)-funded resource, has created a standardized way of evaluating disease genes and variants in these genes based on solid literature and other facts. "ClinGen works in disease domain groups," he says. "The neuromuscular group, which I lead, includes expert panels for muscle diseases, inherited peripheral nerve disorders, and ALS. For some variants, there is overwhelming peer-reviewed evidence, for others, there simply isn't. Over time, the evidence will improve and hopefully reduce the clinical burden of VUS."

A final major VUS challenge is how to address the lack of specific result with patients. "If a patient report has a VUS in it, then you can't tell the patient that you found their gene and you can't say you have the solution," Dr. Zuchner says. It may be that the most accurate response a physician can give is that they are not able to find the patient's disease gene, but that may change in the future with additional analysis of their data.

"It's not the situation that you want," he says. "But that's why work must continue to improve it."