Genetic sequencing alone doesn't offer a true picture of human disease

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Despite what you might have heard, genetic sequencing alone is not enough to understand human disease. Researchers at Duke University Medical Center have shown that functional tests are absolutely necessary to understand the biological relevance of the results of sequencing studies as they relate to disease, using a suite of diseases known as the ciliopathies which can cause patients to have many different traits.

"Right now the paradigm is to sequence a number of patients and see what may be there in terms of variants," said Nicholas Katsanis, Ph.D. "The key finding of this study says that this approach is important, but not sufficient. If you really want to be able to penetrate, you must have a robust way to test the functional relevance of mutations you find in patients. For a person at risk of type 2 diabetes, schizophrenia or atherosclerosis, getting their genome sequenced is not enough – you have to functionally interpret the data to get a sense of what might happen to the particular patient."

"This is the message to people doing medical genomics," said lead author Erica Davis, Ph.D., Assistant Professor in the Duke Department of Pediatrics, who works in the Duke Center for Human Disease Modeling. "We have to know the extent to which gene variants in question are detrimental – how do they affect individual cells or organs and what is the result on human development or disease? Every patient has his or her own set of genetic variants, and most of these will not be found at sufficient frequency in the general population so that anyone could make a clear medical statement about their case."

Davis, working in the lab of Katsanis, and in collaboration with many ciliopathy labs worldwide, sequenced a gene, TTC21B, known to be a critical component of the primary cilium, an antenna-like projection critical to cell function.

While a few of the mutations could readily be shown to cause two main human disorders, a kidney disease and an asphyxiating thoracic condition, the significance of the majority of DNA variants could not be determined. Davis then tested these variants in a zebrafish model, in which many genes are similar to humans, and showed that TTC21B appears to contribute disease-related mutations to about 5 percent of human ciliopathy cases.

The study, which appears in *Nature Genetics* online on Jan. 23, shows how genetic variations both can cause ciliopathies and also interact with other disease-causing genes to yield very different sets of patient problems.

Katsanis, the Jean and George Brumley Jr., M.D., Professor of Pediatrics and Cell Biology, and Director of the Duke Center for Human Disease Modeling, is a world expert in ciliopathies such as Bardet-Biedl Syndrome, in which the primary cilium of cells is abnormal and leads to a host of problems. About one child in 1,000 live births will have a ciliopathy, an incidence that is in the range of Down's syndrome, said Katsanis.

"By sequencing genes to identify genetic variation, followed by functional studies with a good experimental model, we can get a much better idea of the architecture of complex, inherited disorders," Katsanis said. "Each individual with a disease is unique," Davis said. "If you can overlay gene sequencing with functional information, then you will be able to increase the fidelity of your findings and it will become more meaningful for patients and families."

It will take more laboratories doing more pointed studies like this one to get a fuller picture of the ciliopathies and other diseases, Davis said.

Katsanis noted that it will take true collaboration within many scientific disciplines as well as scientific finesse to get at the true roots of complex diseases.

"Brute force alone – sequencing – will not help," he said. "Technology is of finite resolution. You must have synthesis of physiology, cell biology, biochemistry and other fields to get true penetration into medically relevant information."

Provided by Duke University