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Scientists can now better diagnose diseases with multiple genetic causes

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Scientists at Baylor College of Medicine, Baylor Genetics, the University of Texas Health Science Center at Houston and Texas Children's Hospital are combining descriptions of patients' clinical features with their complex genetic information in a unified analysis to obtain more precise diagnoses of complex diseases, particularly those that involve more than one gene causing the condition.

The researchers anticipate that improved clinical and genetic diagnoses could lead to patients receiving more effective treatments and families benefiting from needed counseling. The study is published in the *New England Journal of Medicine*.

"One of the main interests of our lab is to better understand the impact of genetic variation on human health and disease," said co-first author Dr. Jennifer Posey, assistant professor of molecular and human genetics at Baylor.

"Traditionally, physicians have spoken of a unifying diagnosis, meaning that genetic conditions are due to mutations in only one gene," said co-first author Dr. Tamar Harel, who was a genetics fellow at Baylor when she was working on this study and currently is a geneticist at Hadassah Medical Center in Israel. "Yet, we see here that two or more genes can be involved in a disease and produce a complex clinical picture. For many in the field, this is a revolutionary idea."

The challenge of diagnosing diseases with multiple genetic causes

The researchers used whole exome sequencing to analyze all the genes in the genomes of nearly 7,400 unrelated patients with the goal of identifying the genetic cause of their conditions. They found a genetic cause in 2,076 of the 7,374 patients (28 percent); among these patients, 101 (approximately 5 percent) had two or more disease genes involved. If an individual has multiple defective genes, he or she may present with a complex set of clinical features that may lead to an imprecise diagnosis.

"Clinically, multiple genetic causes can be missed because a patient may present with characteristics that overlap those of two different conditions, so the patient can be diagnosed with one or the other," said Posey. "Alternatively, a patient's clinical characteristics may not match those of any described condition, so the patient may be diagnosed with what is thought to be a new condition."

"In these situations, we, as physicians, have to think of the possibility that more than one gene might be involved in the patient's disease," said senior author Dr. James R. Lupski, Cullen Professor of Molecular and Human Genetics at Baylor. "Our study shows the limitations of defining a disease according to what we see in the clinic alone. Our work shows the need to consider that a patient may have two or more genetic diseases, not one, and to send for a genomic test to help sort out the patient's condition and causes of it."

Paving a future toward more precise multiple genetic diagnoses

"One of the contributions of our work involves utilization of a structured

phenotype ontology," said Posey. "This computational tool allows us to model complex clinical features (phenotypes) that can result when more than one gene is involved, in order to better understand, from the perspective of the physician, how such cases may present in the clinic."

Furthermore, Dr. Regis James, now at Regeneron Pharmaceuticals, and Dr. Chad Shaw, associate professor of molecular and human genetics at Baylor, both contributors to this work, previously created OMIM Explorer, a tool that helps analyze genomic data in the context of the clinical characteristics of the patient.

"It provides a more complete perspective of how genes and physical traits relate to each other," said Lupski.

"My colleagues and I anticipate that in the future, geneticists, clinicians and mathematicians will work together using genetic and clinical information to make diagnostic and therapeutic decisions," said Harel.

"This paper reinforces the need to identify the diagnosis for patients with undiagnosed rare diseases and demonstrates that an unbiased comprehensive approach, such as whole exome sequencing is essential in the 5 percent of cases where two or more disorders are present," said Dr. Ada Hamosh, Dr. Frank V. Sutland Professor and clinical director at the McKusick-Nathans Institute of Genetic Medicine (IGM), and scientific director of Online Mendelian Inheritance in Man (OMIM) at Johns Hopkins University, who was not a contributor to this study.

"This work is especially relevant in the era of precision medicine," said senior co-author Dr. Yaping Yang, senior director of Baylor Genetics and associate professor of molecular and human genetics at Baylor. "I am very happy that in addition to providing molecular diagnoses to individual patients, our data is contributing to a better understanding of genetic disorders and genomic medicine."

"Helping patients and their physicians to discover the underlying genetic mechanism of their condition is our most important priority," said co-author Dr. Christine M. Eng, professor of molecular and human genetics at Baylor and chief quality officer and chief medical officer at Baylor Genetics. "The data provided by this study compels us to continue the search for genetic contributions to a patient's overall clinical presentation."

More information: Jennifer E. Posey et al. Resolution of Disease Phenotypes Resulting from Multilocus Genomic Variation, *New England Journal of Medicine* (2016). DOI: 10.1056/NEJMoa1516767

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