Clinical gene discovery program solves 30 medical mysteries

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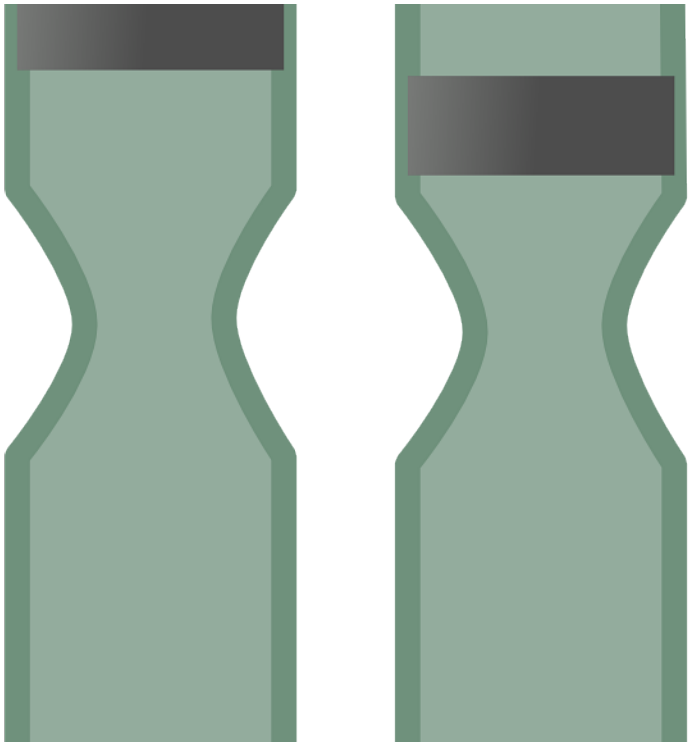

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A table in a recently published paper tells the story of 30 families who have, sometimes after years of searching, finally received an answer about the condition that has plagued one or more family members. The Brigham Genomic Medicine (BGM) program, an integrated, multi-disciplinary clinical and research program, brings together world-class

experts from across Brigham and Women's Hospital as well as the entire Harvard-affiliated community to help in the search for these answers, using the power of whole genome sequencing or whole exome sequencing, in combination with other genomic methods, to scour the genome for new genetic culprits. The results of this exhaustive search and analysis can yield not only a diagnosis for a patient or family that has been desperately searching for one but may also offer information that could help guide novel treatment or predict if other family members are at risk. In a recent paper published in *Genomic Medicine*, the BGM team describes its program, one the team hopes will serve as a model for other academic medical centers or institutions that are endeavoring to solve medical mysteries using genomic sequencing and the power of scientific crowdsourcing.

"Every patient can be an important subject for discovery," said lead and corresponding author Alireza Haghighi, MD, DPhil, a faculty and scientist in the Department of Medicine, Brigham and Women's Hospital, and Harvard Medical School, and the lead clinical molecular geneticist of Brigham Genomic Medicine. "One single patient or family may lead us to know more about the genes and what they do, and maybe ultimately uncover new therapeutic pathways."

Researchers have been working for decades to unravel how genetics contributes to disease. Today, while studies of thousands of people have uncovered many disease associations, the function of much of the genome remains unknown. The BGM program's approach takes advantage of state-of-the-art genomic technologies and access to genomic information from healthy individuals to filter out non-disease-causing genes and mutations and focus in on genetic alterations that might be driving an individual's disease.

"We hope that some of the findings may ultimately inform drug discovery efforts," said Haghighi.

The BGM program has developed new computational analysis pipeline—a workflow that uses computer programming for genomic analysis. "We have developed software, algorithms, and methodology optimized for the effective analysis of genome sequencing data and for the discovery of new disease-causing genes," said Shamil Sunyaev, Ph.D., distinguished chair in Computational Genomics, a professor of medicine at BWH and a professor of biomedical informatics at Harvard Medical School.

The team also uses a crowdsourcing strategy. "While one analyst is responsible for each case, an interdisciplinary team that includes clinical experts from many different fields analyzes the data independently and interactively and discusses the findings. Our approach provides an opportunity for faculty across the Harvard community to look at both the genetic data and clinical information and contribute insights on these cases to help find a cause," said Joel Krier, MD, clinical chief, and a faculty scientist in the Division of Genetics, Brigham and Women's Hospital and Harvard Medical School.

Added Haghighi, "This approach reduces cost and time. Cases like these can be very expensive to solve when patients must go from one expert to another in search of answers, undergoing many different diagnostic procedures. We think that crowdsourcing provides an important opportunity to help these patients and the health care system."

So far, the program has successfully identified culprit genes for 30 families. Patients are referred to it by their physician after their doctor has tested for known genetic causes of disease and been unable to find a cause. "After the BGM team performs genomic sequencing, analysis and crowdsourcing, we share their findings back with the patient's physician and strategize together about a new or improved clinical management plan for the patient," said Krier.

In some cases, findings can yield answers for an entire family. As reported in a paper published by the BGM team in The *Proceedings of the National Academy of Sciences*, one family has received critical information about the cause of a rare aortic disease, with implications for diagnostics and treatment going forward.

"Family members carrying the disease-causing mutation are now being monitored for aortic dilatation, which represents a significant therapeutic benefit to the family, enabling earlier interventions," said Krier. Haghighi and colleagues hope that the findings from this family and others will lead to insights for therapeutic targets for the development of new treatments.

A distinctive feature of BGM is its focus on undiagnosed cases that are refractory to standard diagnostic approaches. In addition, the program provides an integrated and continuous pathway from case ascertainment to treatment. "While there are research programs that look for gene-disease associations, taking this approach in the practice of genomic medicine represents a new model," said Richard Maas, MD, Ph.D., chief of the Division of Genetics at Brigham and Women's Hospital, and a professor of medicine at Harvard Medical School. "By performing genome sequencing for gene discovery in a clinical setting with clinicians, we hope to improve individual treatment plans or therapeutics. Our model can be readily adapted by other academic medical centers around the world."

More information: An integrated clinical program and crowdsourcing strategy for genomic sequencing and Mendelian disease gene discovery, *npj Genomic Medicine* (2018). DOI: 10.1038/s41525-018-0060-9

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