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As new data wave begins, a gene study in one disease discovers mutations in an unrelated disease

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Often enough, in science as in life, unexpected knowledge has a personal impact. Researchers seeking rare gene variants in just a few individuals with attention-deficit hyperactivity disorder (ADHD) discovered that one patient had a novel combination of two mutations. Those mutations caused a different disease, unrelated to ADHD—a blood disorder called idiopathic hemolytic anemia.

Although the man had long contended with the blood disease, "idiopathic" meant that physicians were unable to determine the cause of his particular anemia—until now, say authors of a new study.

As gene-sequencing costs continue to drop as a result of new technology, the authors predict "a coming wave of unrelated findings and the resolution of 'idiopathic' diseases." In its wake will be new ethical and clinical implications—such as how and when to best share these findings with people who provide their own DNA for the research.

Rapid improvements in analytical tools are enabling researchers to more frequently sequence whole genomes of individual patients, said study leader Gholson J. Lyon, M.D., Ph.D., a psychiatrist and principal investigator in the Center for Applied Genomics at The Children's Hospital of Philadelphia. "As we sequence whole genomes, we will find new mutations unrelated to the disease under investigation," he added. "How do we handle this information, especially when it doesn't lend

itself to immediate action by a patient and physician? This is an issue that is coming to the forefront with current advances in genetic knowledge."

Lyon, and co-corresponding author Kai Wang, Ph.D., published the study online July 15 in the journal *Discovery Medicine*. (Formerly at The Children's Hospital of Philadelphia, Wang is now at the University of Southern California.)

In the current study, Lyon and colleagues performed genetic analysis in a Utah family in which a father and two sons have a severe form of ADHD. All three had responded to a stimulant drug in a clinical trial, but ADHD is a complex disorder, with many different genes thought to be involved in conferring susceptibility to ADHD. Hence the researchers sought to identify specific mutations affecting this family.

In this collaboration among scientists at Children's Hospital, BGI-Shenzhen and the University of Utah, the researchers first captured most of the exome, the protein-coding sequences of DNA from each patient's genome. Then they sequenced and analyzed the exomes to identify gene mutations with a likelihood of causing disease.

The study team identified several rare gene variants from the family members that might contribute to ADHD, but they have not yet been able to prove clear-cut causation. However, they did find other mutations that appear to cause chronic anemia in one family member.

The man, a young adult, had been plagued his whole life with chronic anemia, had suffered abdominal pain and jaundice, and had undergone surgeries to remove first his gallbladder, then his spleen. "He had been told that he had 'idiopathic hemolytic anemia,' which basically means, 'your red blood cells are bursting open for reasons we do not understand,'" said Lyon.

The exome sequencing quickly pinpointed two separate, rare mutations in PKLR, a gene that makes pyruvate kinase, an enzyme in which defects have previously been implicated as one cause of hemolytic anemia. This form of anemia is recessive, so the man received one mutation from his mother, the other mutation from his father. This is the first scientific report of both mutations occurring in the same person.

After consulting with the University of Utah institutional review board (IRB) that oversees human subject research, Lyon informed the patient's hematologist of the results, with a request to follow up the findings and offer genetic counseling. "If this information had been available many years earlier, the patient may have received treatment or been advised to take preventive measures that could have possibly avoided complications, including the need for surgical removal of his spleen," said Lyon, adding, "This illustrates the kind of medical information that will become more widely available as the pace of genetic discovery increases."

With appropriate genetic counseling, the genetic information can be helpful to this patient, as he is extremely unlikely to pass on anemia to any future children, because of the recessive nature of the illness and the rarity of these specific mutations.

"There is considerable debate among medical geneticists and medical ethicists about whether genetic research results should be returned to participating research subjects," said Lyon. "In this case, we informed the patient's doctor so that they could decide how to proceed."

Medical practice is still evolving on the questions of how to use this information, added Lyon. "For now, it remains a challenge to quickly discover causative mutations for complex multigene diseases. However, the whole genetics field is moving toward doing whole-genome sequencing to find disease-causing mutations, and in the future, a

person's full genome sequence will probably be linked to his or her medical records. Researchers and clinicians will be learning how to handle this information."

More information: "Exome Sequencing and Unrelated Findings in the Context of Complex Disease Research: Ethical and Clinical Implications," Discovery Medicine, published online July 15, 2011. Open access journal, freely available at www.discoverymedicine.com

Provided by Children's Hospital of Philadelphia