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Mom, dad and kids undergo novel genome analyses for medical risks in new study

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Stanford University School of Medicine researchers have predicted the inherited health risks of a four-person family by analyzing their whole genome sequences. With the DNA sequences of both parents and children, the team was able to better check for sequencing errors and more accurately predict how individual genetic variants affect each family member's risk for disease.

The project improved computational tools that provide medical interpretation of genomes, which includes disease-risk prediction and how an individual would respond to common medications. "With the continuing decline in the cost of genome sequencing, routine genome analysis could be the future of medicine," said Euan Ashley, MD, assistant professor of cardiovascular medicine and senior author of the study.

The study, to be published Sept. 15 in PLoS Genetics, will be the second reported analysis of a four-person family of genomes, but the first to include a whole-genome interpretation of a family's medical risks. The previous report, by another group of researchers, focused on the genetic cause of a rare disorder affecting the children of that family. Ashley also published a study last year that involved the first whole-genome medical risk assessment for an individual, and the methods developed in that paper provide the basis for this new study.

"This work pushes the boundaries of our understanding of personal genomes by adding the strength of family genetics to the technology of

genomics," said Rochelle Long, PhD, director of the National Institutes of Health Pharmacogenomics Research Network. "The advance promises a new era of personalized medicine in which people will be able to make informed decisions about medical treatment based on their individual genetic risks."

Human genomes carry two copies of each gene — one inherited from each parent. With a family of genomes, the researchers could determine exactly which parent had donated a given copy of a gene to their offspring, allowing them to better calculate the severity of health risks when many variants were found together.

"Sequencing families leads to better genetic data and will be an important part of analyzing genomes for medicine," said lead author Frederick Dewey, MD, cardiology fellow and postdoctoral researcher.

The related set of genome sequences also allowed the scientists to locate, with the most precision reported to date, where along the DNA strand the parents' chromosomes had mixed together before being passed to the next generation — a diversity-generating process known as genetic recombination. The daughter of the family, who, along with her father, is a co-author of the study, initiated the genetic recombination analysis as an at-home project.

A familial predisposition to blood clotting led the West family of Cupertino, Calif., to explore their genetics, initially on their own. In 2003, father John West suffered two pulmonary embolisms (blood clots in the lung) and he wondered if he had passed any clotting risks to his children. Genotyping analysis from the personal genomics company 23andMe revealed that the daughter, Anne, had inherited the same risks. Now armed with the much more extensive knowledge of her genetic risks derived from whole-genome sequencing, she can avoid the problems experienced by her father with some simple lifestyle changes

at this time and perhaps a drug like aspirin later in life.

As a high school student, Anne West calculated the frequency of genetic recombination in her family, first with snippets of genetic information from the 23andMe data and then with the family's full genome sequences from biotechnology company Illumina. "The amount of data is vast and intimidating but if you analyze the data question by question, the next step in the investigation usually reveals itself," she said. She also identified the origin and implications of some disease variants in the family's genomes and presented her work at a national scientific conference, which landed her an internship in a genetics lab at Harvard.

Still, the family wanted to know more than one busy teenager armed with Excel spreadsheets could manage. So John West approached Stanford cardiologist Ashley and colleagues for help. Last year, Ashley led a team to publish the first medical interpretation of a complete human genome and the tools developed in that study had been significantly enhanced to explore the West family's disease risks. One important component of the genomic analyses is the large, hand-curated databases that link genetic information with health. The lab of Atul Butte, MD, PhD, associate professor of systems medicine in pediatrics, developed Varimed, a database of genetic variants associated with diseases, and the lab of Russ Altman, MD, PhD, professor of genetics and of bioengineering, developed PharmGKB, a database of genetic variants associated drug response. Butte and Altman are co-authors of the paper.

To make the best use of those databases, the authors created new reference genomes against which an individual's genome can be compared.

Typically, human genetic information is checked against the human reference genome, a composite of several anonymous donors' DNA that

does not have the most common DNA sequence at every position. In fact, the reference genome lacks the most common variant at 1.6 million genomic positions, 4,000 of which affect disease risk. "Because the reference-genome donors are real people, they have some genetic risks," said Ashley. "If you compare a new genome against that reference genome, you will miss the places where that reference genome and the new genome have the same risk variants."

For instance, the human reference genome contains versions of a clotting gene known as the Factor 5 Leiden variant, which increases the risks of blood clots. Both Anne West and her father have this variant, and if either had carried two copies of that same variant, typical genome analysis would not have identified that risk.

"We found 23 instances in the human reference genome where there were rare variants associated with large disease risk, such as the Factor 5 Leiden variant. Using the current reference genome, these variants wouldn't have been identified in any individual's sequenced genome if they had two copies of the mutation," said Dewey.

To work around this problem, Dewey used published genetic data from hundreds of unrelated people (part of the 1,000 Genomes project) to develop three, ethnicity-specific, synthetic reference genomes, which contain the most common variants for each group. Comparing an individual's genome to one that is ethnically matched and contains the most common variants aids the detection of rare disease-risk variants and reduces the number of errors in determining each person's exact genome sequence, the researchers found.

"Sequencing people of more diverse backgrounds is going to be extremely important in moving forward with the application of these genetic risk predictions to other populations," said Dewey.

Specifically for the Wests, the team identified multiple variants in genes related to clotting. They also identified the exact physician-determined dosage of anticoagulants that John West was already taking, and predicted the dosage that Anne West may one day need.

"Genome sequencing is impacting medicine right now," said Ashley. When the Wests had their genomes sequenced, it cost about $40,000 each. Now, companies offer the similar services for around $4,000 and that price is expected to fall as technologies improve. That means many more people will likely have their genomes sequenced soon, but without some analysis they won't mean much more than alphabet soup. "We believe medical genome interpretation could revolutionize medicine," said Ashley. "So many people have contacted us asking for help to analyze their genomes, but as an academic lab, we simply don't have the bandwidth. Industry will have to get involved." To that end, Ashley, Butte, Altman, John West and Stanford co-author Mike Snyder, professor and chair of genetics, have started a biotech company called Personalis through which they plan to offer management and analysis of whole-genome sequencing.

For the West family, the experience provided more than just medical information. "I think we may learn more about the results medically in the years to come as we are better able to analyze the genome, but the educational opportunity for Anne has been terrific right up front," said John West.

More information: Dewey FE, Chen R, Cordero SP, Ormond KE, Caleshu C, et al. (2011) Phased Whole-Genome Genetic Risk in a Family Quartet Using a Major Allele Reference Sequence. PLoS Genet 7(9): e1002280. doi:10.1371/journal.pgen.1002280
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