



A Family Learns the Secrets of Its Genomes

The findings demonstrate how genome analysis could guide health-care decisions for healthy people.

By Emily Singer

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In November 2009, the West family embarked on an unusual family project. Parents John and Judy and teenagers Anne and Paul each had their genomes sequenced, and enlisted a team of scientists at Stanford University to interpret the meaning of the combined 24 billion letters of DNA in those genomes.



Sequence team: John West, front, had his family's genome sequenced. A team of Stanford researchers, including Euan Ashley, middle, and Rick Dewey, back, helped interpret it.

The findings, published today in the journal PLoS Genetics, are the first attempt to analyze the genome of a healthy family, a feat that gives family members clues to their future risk of disease, points to lifestyle changes that may help mitigate those risks, and highlights the drugs that are most likely to help or harm them. One of the major benefits of sequencing a family is that it generates much more accurate data, by allowing scientists to filter out sequencing errors. More broadly, the project hints at the future of personal genomics, capturing both the potential for preventive medicine and the challenges in interpreting the meaning of the genome for people who are largely healthy.

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A major part of the project was developing streamlined tools for interpreting the vast complexity of the human genome. Such tools are becoming increasingly important as the cost of sequencing plummets—from about a million dollars per genome in 2007 to between \$4,000 and \$10,000 now—and as the number of sequenced genomes available for analysis grows. (John West, formerly head of Solexa, a sequencing startup bought by Illumina in 2007, paid Illumina \$40,000 per genome in 2009.)

“Data is coming out thick and fast, and as a community of scientists and clinicians, we need to think about what we’re going to do with that,” says [Euan Ashley](#), a cardiologist and head of the Stanford team. After helping colleague [Stephen Quake interpret his genome](#) last year—a project that involved synthesizing decades’ worth of scattered research on the human genome and figuring out how to apply it to a living, breathing person—Ashley’s team began getting calls from both individuals and researchers, and asking for aid in interpreting genomes.

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Indeed, genome sequencing is at something of a tipping point. The cost of sequencing is now on par with diagnostic tests that analyze just a few genes, meaning that for those suspected of having inherited disorders, it now makes economic sense to sequence the entire genome rather than just suspect genes. “Even if these highly predictive and actionable [variations] are considered rare” collectively, “everyone is at risk and should be just as willing to spend on this as on fire insurance and other unlikely contingencies,” says George Church, a geneticist at Harvard who participated in both the West and Quake projects. Church’s group has done similar analysis of 64 genomes as part of the personal genome project, a nonprofit effort to sequence and interpret thousands of genomes.

Ashley, West, and two other collaborators have since founded a startup called [Personalis](#) to commercialize the tools they have developed. The company’s initial focus will be on analyzing genome sequences for researchers, but it ultimately aims to move into the clinical realm. “What’s going to happen when there are thousands of families like us?” says West. “We agreed it would make sense to set it up as a company.”



Family genome: The West family, shown here on vacation in Alaska, is the first healthy family to have all its members' genomes sequenced and interpreted for medical purposes.

West got his first taste of the power of genomic medicine in 2003, after suffering a pulmonary embolism, a blood clot that migrated to his lungs. He learned he had a mutation in a gene called Factor V Leiden that leads to abnormal blood clotting and is found in about 2 to 3 percent of the U.S. population.

"It turns out you can deal with it quite easily if you know about it," says West, who made simple lifestyle changes after discovering the mutation, avoiding certain foods and making sure to move around on long flights. "Finding out about this risk by getting an e-mail with your genome sequence is better than finding out by ending up in the hospital," he says.

West wondered whether similar insights could be found in his genome, or those of his family members.

The West family are among the first users of 23andMe, a direct-to-consumer company that offers genetic analysis of some of the most common genetic variations. They learned that John had passed on his blood-clotting mutation to daughter Anne. She also put the knowledge to use in making her own health-care decisions. When her physician suggested birth-control pills to clear up her skin, Anne knew she shouldn't take estrogen-based medicines, which can increase clotting risk.

"We all know we have diseases that run in the family," says Ashley. "What the sequence allows us to do is know which risks you have inherited and from which individual."

Once the cost dropped low enough, the Wests took the full plunge into whole-genome sequencing. One of the major benefits of sequencing a family is that it generates much more accurate data. By comparing intergenerational genomes, scientists can identify likely errors by looking for spots where the child's genome differs from the parents'. Last year, Leroy Hood and collaborators sequenced a family of four in an attempt to identify the genetic variations underlying a rare

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Accuracy is really upgraded by having family-based sequencing," says Eric Topol, head of the Scripps Translational Science Institute, in San Diego, who was not involved in the study. Topol predicts this approach will become more common as whole-genome sequencing grows.

Most of the medically relevant sequencing efforts to date have been focused on children with rare genetic diseases; the goal is to find the cause of the disease—typically a single mutation—rather than to sift through the meaning of the rest of the genome. But Ashley's team was tasked with approaching the genome as a primary-care physician of the future might do it: looking for as much useful medical information as it could, and using it to recommend ways to prevent health problems whenever possible.



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variations that can be linked to serious inherited disorders, such as cystic fibrosis. It used databases developed by two members of the team, Atul Butte and Russ Altman, which incorporate research collated from thousands of scientific papers.

The team discovered that both Anne and John share a second variation linked to a blood-clotting disorder. However, it's not yet clear whether this mutation contributed to John's previous medical problems, highlighting one of the challenges in genome interpretation. "The stumbling block is putting together all the different variants associated with disease," says Ashley. "We have a good estimation of individual effects, but what's harder is trying to work out the effect of multiple variants."

Mother Judy discovered she had a mutation linked to risk of carotid stenosis, a narrowing of the artery that links the heart and brain, which she had passed on to both children.

Some scientists, physicians, and policymakers have raised concerns that genetic testing that highlights increased risk for common diseases will lead people to get unnecessary diagnostic tests, taxing an already overburdened medical system. However, West believes that predictive testing will actually help allocate medical resources more effectively and prevent costly complications, as well as the need for more serious treatment later in life. Hospitalization and treatment for stroke, heart attack, or embolism costs tens of thousands of dollars. "Out of thousands of possible tests," genetic testing highlights a handful to keep an eye on, he says.

One of the areas of medicine that genomic analysis may overhaul most quickly is pharmacology. Researchers have done extensive analysis on the effect of variations in genes that metabolize different drugs. West, for example, takes the blood thinner warfarin daily, a drug that has to be carefully dosed in order not to trigger excessive bleeding. By analyzing variations in genes involved in drug metabolism, researchers were able to predict the optimal dose that West had arrived at several years earlier through a laborious trial-and-error process. With this type of analysis, "you can start to match up conditions in a family and guidance for drugs," says Topol. "That's unique and noteworthy."

As part of the analysis, researchers developed an alternate version of the reference sequence—the genome sequence generated in the human genome project, which geneticists use to compare new genomes. "It doesn't capture lot of genetic variation, and has no ethnic information," says Frederick Dewey, one of the researchers on the project. They used the HapMap and the 1,000 Genomes Project, two international projects designed to catalogue human genetic diversity, to create a more comprehensive reference sequence. 

by Emily Singer



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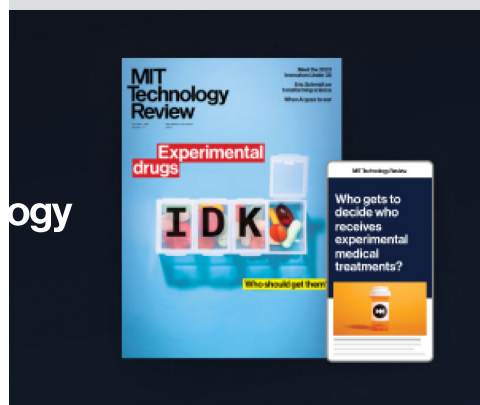
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