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Is DNA from mom or dad? New technique will accelerate personalized medicine

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A new technique successfully takes on a longstanding challenge in DNA sequencing – determining whether a particular genetic sequence comes from an individual's mother or father. The method, described in a Ludwig Cancer Research study in *Nature Biotechnology*, promises to accelerate studies of how genes contribute to disease, improve the process of matching donors with organs and help scientists better understand human migration patterns.

"The technique will enable clinicians to better assess a person's individual risk for disease. It is potentially transformative for personalized medicine," says Bing Ren, Ludwig scientist at the University of California, San Diego School of Medicine, who led the research on the new technique, called "HaploSeq."

"Current sequencing technologies are fast and rapidly getting cheaper – an individual's genome can now be sequenced in about a week for $5,000," says Ren. "In the not too distant future, everyone's genome will be sequenced. That will become the standard of care." But, he explains, "There has been a problem with this scenario." Except for the sex chromosomes, everyone has two copies of each chromosome. One copy comes from mom, and the other from dad. Current techniques cannot distinguish between the two copies of each gene and, therefore, are not very good at determining whether particular genetic differences, such as a single-letter change in the DNA, originate with an individual's mother or father – muddying genetic analyses.

Ren's new technique, a mixture of molecular biology and computational biology approaches, bypasses this problem. The method enables researchers to quickly determine which genetic variants occur together on the same stretch of chromosome and, therefore, came from the same parent. "This advance has direct implications for the utility of genomics in clinical practice and will also have profound effects on genetic research and discovery," says Ludwig scientist Siddarth Selvaraj, who contributed to the study with Ren and fellow Ludwig researcher Jesse Dixon.

More immediately, the technique will enable clinicians to better assess a person's individual risk for disease, a cornerstone of personalized medicine. For instance, people at risk for a disease such as cancer often have more than one DNA mutation. HaploSeq could enable clinicians to determine if the two mutations are on the same chromosome or on different chromosomes, which can help in risk assessment – for instance, risk may be reduced if two mutations are on the same chromosome, since the 'good' chromosome can often compensate.

Similarly, the method, with further honing, has the potential to refine the currently cumbersome process of determining whether there is a genetic match between an organ donor and recipient. A large number of genes contribute to compatibility between donor and recipient, but there is a lot of genetic variability in these genes. The new technique could help determine whether DNA differences between donor and recipient are likely to be a good match. "This will require more study," says Ren, "but by creating a DNA database, it may be possible to more accurately and expediently pair recipients and donors."

The new method will also help researchers analyze human migration and determine ancestry from their DNA sequences. "In principal," says Ren, "you could compare your genetic sequence to your neighbor's and ask if you have any recent ancestors in common. With our technique we can

study each individual and how they relate to other individuals. As we accumulate data from many individuals we can more precisely determine their relationships." Such findings will also bolster an ongoing international project to assess worldwide human genetic variation, the HapMap project.

One advantage of the new technique is that it builds on common sequencing technologies and should be easily adapted for use by clinicians and researchers alike. Says Ren, "I anticipate that this new method will be quite widely used."

More information: Whole-genome haplotype reconstruction using proximity-ligation and shotgun sequencing, DOI: 10.1038/nbt.2728

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