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Poor in vivo validation may cause inaccurate infertility diagnoses

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Infertility can have genetic causes, but pinpointing the culprit mutations is difficult because fertility and reproduction are controlled by many genes. These genes also carry many harmless but suspicious mutations in

different people, making it hard to spot the truly damaging ones.

In a study published July 17 in *Proceedings of the National Academy of Sciences*, a team led by John Schimenti, professor of genetics in the Department of Biomedical Sciences, in the College of Veterinary Medicine, tested the accuracy of existing methods used to predict the genetic variation that cause infertility.

Getting an accurate interpretation of genetic variation is crucial for giving patients the right diagnosis and recommendations.

"Interpreting the functional impacts of genetic variation is challenging," Schimenti said, "but profoundly important for clinical management and genetic counseling."

When scientists want to identify the genetic mutations responsible for a trait, they use a combination of computational tools and molecular techniques. Typically, complex algorithms analyze the DNA sequence of a patient, and classify the patient's genetic variation based on its likelihood to cause disease.

Most of the variation in our DNA is either classified as benign or as "variants of unknown significance" (VUS).

"A mutation that causes infertility will exist within a background of multiple VUS in candidate genes," Schimenti said. "It is difficult to conclusively implicate any single variant as being responsible for infertility."

For many traits, like rare diseases and cancers, a panel of experts in specific disease areas then examines the computational predictions. The experts search if other evidence—for example, published laboratory experiments—confirm the predictions. This verification process

increases the reliability of the clinical database of genetic variants.

However, there is no such panel for infertility, which requires support and approval from the National Institutes of Health to be established. For reproductive traits, most conclusions are solely based on algorithms' predictions.

Schimenti and his team wanted to assess if computational methods alone provided accurate predictions for infertility-related mutations. They set up an experiment where they examined the fertility of mice engineered to carry human genetic variants in genes essential for male reproduction. They focused on 11 genetic variants that algorithms predicted would disrupt the function of these key fertility genes. Three of these 11 mutations were also observed in men clinically diagnosed with fertility issues.

Out of the 11 mutations predicted to be harmful by algorithms, the researchers found that 10 had no effect on mouse fertility. Only one genetic variant found in a male infertility patient had greatly reduced sperm production in mice.

Schimenti said one reason why in vivo observations did not match the computational predictions is that algorithms are trained on datasets that are inaccurate; if the models are learning on partially wrong data, their predictions are partially incorrect.

"Some studies have demonstrated that nearly half of the rare mutations that were algorithmically predicted to have a negative impact on health did not have the predicted effect," he said.

Another possible reason, he said, is that the computational predictions are not wrong, but that biological systems are resilient against mutations. "Living systems have robustness or redundancies that can mask minor

biochemical or structural defects of proteins," Schimenti said.

Some of these mutations may affect the function of a gene as predicted, but this alone may not be enough to compromise fertility of an organism. Sometimes, genetic variants in a gene only affect a trait when combined with specific variations in other genes.

Schimenti also acknowledges that his experiments tested human mutations in mouse models. "It is possible that mice may be more tolerant to the protein alterations than humans," he said. "It is also possible that the consequences only manifest themselves over longer human lifespans."

Nevertheless, Schimenti's study proves that relying on computational or in vitro experiments alone is insufficient for use as a diagnostic in the clinical setting. These methods used in isolation wrongly label harmless mutations as bad ones, and they fail to identify the genetic factors responsible for infertility in actual patients.

"Computational prediction is only one piece of the evidence," Schimenti said, "and if we don't look at the other pieces, we are bound to make mistakes in our interpretation of genetic variants."

More information: Xinbao Ding et al, In vivo versus in silico assessment of potentially pathogenic missense variants in human reproductive genes, *Proceedings of the National Academy of Sciences* (2023). DOI: 10.1073/pnas.2219925120

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