After stillbirth, new genetic analyses may give parents answers

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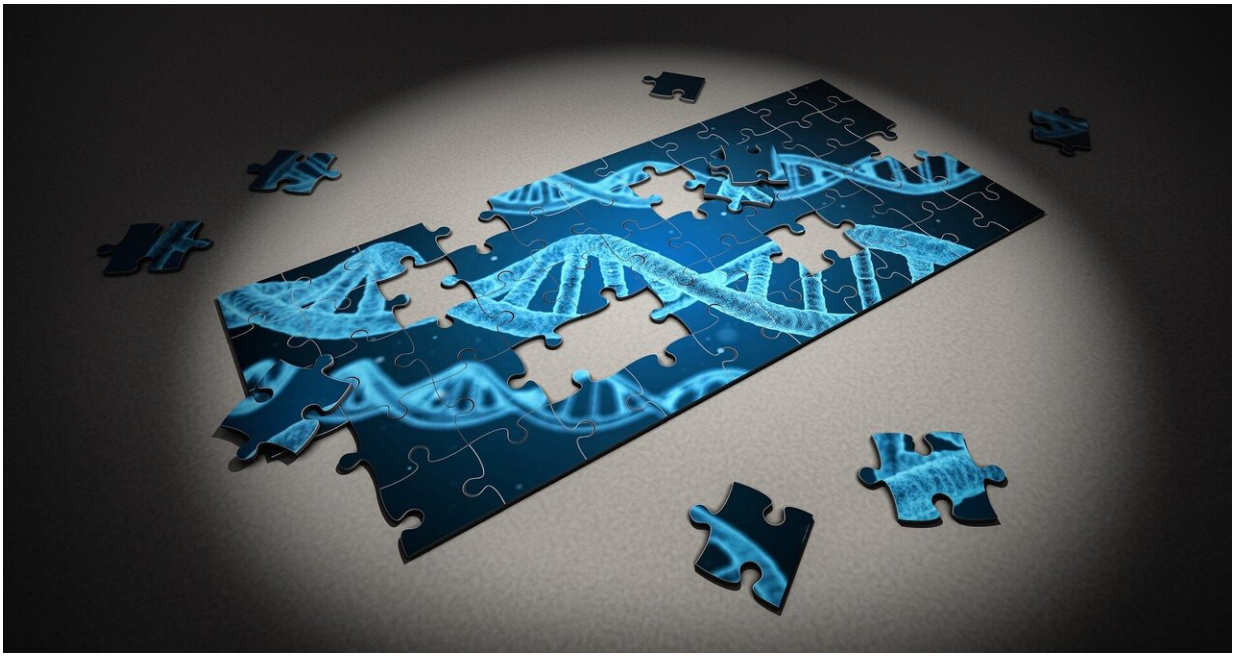

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Columbia researchers have uncovered an array of new genes that cause stillbirth, significantly increasing the understanding of the condition's genetic foundations. The findings suggest that genetic analysis could be used to counsel parents who have previously experienced stillbirth and to unlock new human biology.

Using both standard and advanced analysis techniques, the team led by David Goldstein, Ph.D., and Ronald Wapner, MD, of Columbia University Vagelos College of Physicians and Surgeons (VP&S) identified the likely genetic cause of stillbirth in about one of every 10 cases studied.

"This study shows that careful genetic analyses can often identify the precise genetic causes of stillbirth and demonstrates the importance of diagnostic sequencing in all cases of unexplained stillbirth," says Goldstein, director of the Institute for Genomic Medicine at Columbia University Irving Medical Center. "Of equal importance, the work highlights how little we currently understand about the biology of stillbirth and the role that genomic analysis can play in helping us understand it."

The study was published online today in the *New England Journal of Medicine* by the Columbia team. Kate Stanley, MS, a research associate in the Goldstein lab, and Jessica Giordano, MS, a research genetic counselor in the reproductive genetics division of the Department of Obstetrics & Gynecology at VP&S, were co-first authors of the study.

Presumed Genetic Underpinning, but Few Studies

Stillbirth (the in utero death of a fetus after 20 weeks' gestation) occurs in approximately one in 100 pregnancies and is about 10 times more common than sudden infant death syndrome.

But in the majority of cases, the cause of stillbirth is unknown. Some have been linked to maternal medical conditions such as infection and preeclampsia; 10% to 20% are attributed to large and easily detectable chromosomal abnormalities. Only a few genes have been implicated.

"Unlike postnatal childhood conditions that are presumed to be strongly

genetic, stillbirth had yet to be systematically analyzed with modern genome sequencing approaches," says Goldstein.

"All too often, we have no explanation to give parents who experience a stillbirth," says Wapner, professor of obstetrics & gynecology. "Not only are they devastated, they're often left to wonder if it's something they did wrong or if it might happen again."

Genomic Sequencing Plus New Bioinformatic Analyses Find Hidden Genetic Causes

Genomic sequencing has been particularly useful in diagnosing otherwise unexplained childhood disorders and fetal structural defects, and the Columbia team used it for the first time to search for genetic variants that cause stillbirth.

The researchers sequenced all protein-encoding genes—where most known disease-causing genetic variants occur—from 246 stillborn fetuses and deployed new statistical analyses to identify the genetic mutations that caused the death of the fetus.

The combination of traditional sequencing and new analytical techniques revealed small changes in 13 genes that caused fetal death; six of the genes had not been previously linked to stillbirth.

"Although these are small changes in only a single site in the genome, they are, in effect, genomic sledgehammers that either dramatically change or knock out essential genes and appear responsible on their own for fetal demise," Goldstein says.

The small genetic changes explained 8.5% of the stillbirths in the study. When combined with a previous analysis of larger genomic alterations in this group, the researchers determined that 18% of the stillbirths had a

known genetic cause.

The analysis also showed a critical difference compared with the study of postnatal genetic conditions.

"Interestingly, some of the changes we found in genes known to cause postnatal diseases and conditions appeared to have more profound effects than the mutations linked to postnatal disease," Goldstein adds.

Clinical Implications

Currently, the analyses required to find causal genetic causes of a stillbirth can be conducted in only a few academic medical centers.

But eventually the findings from this study—and future studies—will help physicians counsel parents and guide clinical care.

"To a woman who's just had a stillbirth, specific knowledge about the cause is critical," Wapner says. "They often blame themselves and some decide not to have any more children."

If the stillbirth can be attributed to a genetic mutation that has only occurred in the fetus, not in the parents, the same problem is unlikely to occur in future pregnancies.

"That knowledge would change the way we would provide care," Wapner says, "and facilitate closure and bereavement for families."

Unlocking New Human Biology

Most genetic diagnostic studies focus on genes already known to cause disease. Because stillbirth has been understudied, however, the team wanted to test whether genetic changes in genes not currently linked to

disease contribute to stillbirth.

For this assessment, the researchers used a bioinformatic tool pioneered by the Goldstein lab that focuses on genes that are under the strongest natural selection in the human population—known as "intolerant" genes. The lab team showed that at least 5% of stillbirths are likely explained by mutations in intolerant genes that are not currently linked to any known human disease.

"These novel disease genes appear to be critical for early human development, and the only way to discover them is through the analysis of fetuses that do not develop," Goldstein says.

"We're opening up new frontiers in biology and the more we understand about basic human development, the more we can potentially intervene."

The study is titled "Causal Genetic Variants in Stillbirth."

Provided by Columbia University Irving Medical Center

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