Genomic Insights into Stillbirth

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Stillbirth, or fetal loss after 20 weeks of gestation, remains a major public health challenge that occurs in approximately 6 per 1000 pregnancies in the United States. Unfortunately, many of these losses remain unexplained, even after standard postmortem evaluation. The use of karyotype and chromosomal microarray may identify a diagnosis in 8 to 13% of miscarried fetuses, although monogenic disorders generally remain elusive because these approaches are insensitive to small genetic changes. This lack of insight into causes of stillbirth impedes attempts to improve perinatal outcomes and contributes to the parental psychological burden. Because sequencing technology and the ability to analyze and interpret genomic data have markedly improved over the past few years, applying these techniques to stillbirth seems logical. However, prior attempts to do so have been limited in their scope and generalizability, and the value of genomic sequencing for unexplained stillbirth remains unclear.

In an article now published in the Journal, Stanley and colleagues seek to further understand genetic contributions to stillbirth. They first address what is seemingly a straightforward question: how many cases of unexplained stillbirth have an underlying monogenic cause? That this question remains unanswered after nearly a decade of experience with clinical exome sequencing reflects the inherent difficulty in designing and executing a study to provide meaningful data. Gathering such data from clinical practice is challenged by barriers to sample acquisition and insurance coverage for clinical fetal exome sequencing, and prior research approaches have involved cohorts enriched for severe anomalies, which has resulted in diagnostic yields of close to 50%. Thus, genomic variation underlying stillbirth, particularly after an uncomplicated pregnancy, continues to be incompletely understood.

In a study involving 246 cases of unexplained stillbirth, Stanley et al. describe the use of exome sequencing to search for disease-causing variants in the coding regions of the genome. Using this technique, the investigators identified a plausible genetic diagnosis in 8.5% of the cases. The lower diagnostic yield observed in this cohort than in prior studies of exome sequencing in fetal death suggests that monogenic mendelian disorders may be less likely to underlie such losses in phenotypically normal fetuses than in those with congenital anomalies. The findings also suggest that other avenues (e.g., non-mendelian models) should be followed to explore the genomics of stillbirth. However, this yield, which is similar to the current clinical standard of chromosomal microarray analysis, supports a role for exome sequencing to investigate fetal or perinatal death. The potential diagnostic yield of exome sequencing for unexplained stillbirth is probably underestimated in this study because of its limitations: the lack of trio sequencing analysis, in which parental sequencing data are used to interpret variants (and thus could identify additional diagnoses and add another 3.7 to 8.1% to the yield, as estimated by the authors); omission of fetal deaths resulting from pregnancy termination, which may be relatively enriched for lethal genetic disorders; and the exclusion of cases with a convincing nongenetic explanation for the fetal loss.
The authors found no difference in diagnostic yield between cases in which a possible cause of stillbirth was identified (e.g., abnormal placentation) and those in which the cause was truly unexplained. This finding suggests a broader role for genomic sequencing in stillbirth to uncover genetic diagnoses that may not be suspected clinically because of the coexistence of a fetal monogenic disorder with either a related or an unrelated maternal or obstetrical condition. In addition, the cases that were sequenced for this report represent a subset of the Stillbirth Collaborative Research Network study, through which additional cytogenetic diagnoses had been previously identified with the use of karyotype or chromosomal microarray. The addition of these cytogenetic diagnoses to the findings for exome sequencing bring the total diagnostic yield of genetic testing for unexplained stillbirth in this cohort to 18%. Thus, the use of genome sequencing rather than exome sequencing may ultimately be considered as a single comprehensive test to detect single-nucleotide variants and small insertions or deletions in coding regions in addition to structural and noncoding variants, some of which may be cryptic even to conventional cytogenetic techniques.

In addition to revealing the potential diagnostic value of exome or genome sequencing, Stanley et al. offer valuable insight into the genomic landscape of stillbirth by suggesting that the depletion of loss-of-function variants in certain genes in adult populations may be due to a critical role for these genes in human development. In the presence of such variants, fetuses are unable to survive. Furthermore, in comparing genomic data from the stillbirth cohort in this study with live-birth cohorts that have structural anomalies or other disorders, the authors observe a relative enrichment of apparently damaging variants in candidate novel disease genes as compared with known disease genes. These findings suggest not only that many genetic conditions remain to be discovered but that the full phenotypic spectrum of many known mendelian disorders is not fully understood without the inclusion of cases resulting in death in utero. Continued evaluation of such cohorts that focuses on so-called lethal phenotypes is needed in order to understand the genomics of human disease. Thus, rather than defining the value of genomic sequencing for stillbirth, Stanley et al. offer a rare glimpse into its powerful potential for understanding life and its genetic limitations at different developmental stages.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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