Diagnostic Exome Sequencing Positively Identified Relevant Alterations in More Than Half of Prenatal Samples Tested

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Abstract:
Diagnostic exome sequencing (DES) has been shown to be a successful option for diagnosing individuals with previously uncharacterized genetic conditions. As turnaround times and out-of-pocket costs for DES continue to decrease, its potential utility within the realm of prenatal diagnosis is growing. We performed a retroactive analysis of the first 7 cases referred to our laboratory for DES following fetal demise or termination of pregnancy. All 7 cases had an indication of multiple congenital anomalies identified by level II ultrasound. In 6 of the 7 cases, the parents had had 2 affected pregnancies, and in 2 of the 7, there was an additional family history of similar or related findings. All 7 samples previously had a normal karyotype analysis, and 5 of the 7 had also had normal or uncertain chromosome microarray results, including one consanguineous family identified to have multiple long contiguous regions of homozygosity. DES was performed on cultured amniocytes or products of conception with the addition of parental DES results used during variant filtering and analysis. Results revealed that DES positively identified relevant alterations in more than half (4/7) of the cases included in the study. Identified diagnoses included osteogenesis imperfecta II (*COL1A2)*, glycogen storage disease IV (*GBE1*), oral-facial-digital syndrome 1 (*OFD1*), and *RAPSN*-associated fetal akinesia deformation sequence. The cases of glycogen storage disease IV and *RAPSN*-associated fetal akinesia sequence were inherited in an autosomal recessive fashion with both parents confirmed to be carriers of the inherited alterations. The fetus affected with osteogenesis imperfecta II was found to have a *de novo* autosomal dominant alteration, and the fetus with oral-facial-digital syndrome 1 was a male found to have a maternally inherited X-linked recessive alteration. Based on the results of this study, we conclude that DES is likely to be a valuable diagnostic testing option for pregnancies with multiple congenital anomalies detected by prenatal ultrasound, however further research is needed to confirm these findings. The findings of this study also underscore the importance of discussing the option of collecting and maintaining DNA samples following cases of pregnancy termination, fetal demise, or perinatal death in pregnancies affected with multiple congenital anomalies and/or a suspected genetic condition. With the availability of DES, providers can now offer a viable testing option for families who wish to determine recurrence risks for future pregnancies and for generations to come.

Abstract Topics:
Perinatal Genetics
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Next Gen sequencing

Learning Objectives:

1. To summarize our findings, which support that diagnostic exome sequencing is likely to be a valuable diagnostic testing option for pregnancies with multiple congenital anomalies detected by prenatal ultrasound.
2. To outline the specific genes and associated conditions that were positively identified in a cohort of seven prenatal cases sent to our laboratory for diagnostic exome sequencing following fetal demise or termination of pregnancy.
3. To recommend that providers discuss the option of collecting and maintaining DNA samples following cases of pregnancy termination, fetal demise, or perinatal death in pregnancies affected with multiple congenital anomalies and/or a suspected genetic condition.
4. To point out that diagnostic exome sequencing results may be helpful in the counseling of families who wish to determine recurrence risks for future pregnancies and for future generations.