Whole Exome Sequencing
Applications in Prenatal Genetics

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KEYWORDS

• Fetal • Exome • Sequencing • Prenatal ultrasonography • Abnormalities

KEY POINTS

- Prenatal whole exome sequencing is emerging as a valuable tool for fetal diagnosis in the setting of sonographic abnormalities.
- Diagnostic rates are variable across studies, with improved rates when trio (proband, mother father) whole exome sequencing is performed.
- Prenatal genetic counseling is crucial for appropriate parental consent for whole exome sequencing.
- There are many ethical considerations, including risks of discrimination, that must be considered when whole exome sequencing is performed.

BACKGROUND

Ultrasonography-detected fetal sonographic abnormalities are identified in 2% to 3% of pregnancies.[1] Genetic diagnosis with amniocentesis or chorionic villus sampling with chromosomal microarray (CMA) and karyotype are routinely offered in these cases. Of cases that undergo diagnostic testing, a karyotype abnormality is found in 8% to 10% of cases, whereas a microdeletion/duplication is identified in another 6%, leaving most families without a specific genetic diagnosis.[2] These families must therefore be counseled based on ultrasonography findings alone. Management decisions thus need to be made from limited information and counseling is challenging because of the broad differential diagnosis and large range of prognoses and expectations. Whole exome sequencing (WES), rather than targeted disease-specific gene panels, is now being studied and used to improve prenatal diagnosis in cases in which structural abnormalities are identified sonographically. Initial studies show that prenatal WES can elucidate the responsible pathogenic variants in an additional 20%[3] to

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80%[4] of cases when standard genetic testing (karyotype and CMA) is normal. The diagnostic yield of prenatal WES is known to be highly dependent on the indication for WES.

WES, unlike whole genome sequencing (WGS), is currently clinically available and focuses on the exons or protein coding regions of the genome only (**Fig. 1**). Exons account for 1.5%[5] of the DNA in the genome, comprising approximately 22,000 genes. Most identified genes implicated in mendelian disease involve the exons.[6] Thus, WES is more cost-effective than WGS. In addition, WES is preferred because the ability to interpret intronic regions of the genome is currently extremely limited. Prenatal WES has the ability to increase diagnostic rates in cases in which fetal anomalies are present and enhance the understanding of pathogenic variants that are developmentally lethal.[7] WES also has the potential to expand known disease phenotypes to the prenatal period. Multiple challenges of prenatal WES include (1) interpreting the vast amount of data in a timely manner; (2) identifying pathogenic variants in diseases with reduced penetrance and variable expressivity; and (3) providing adequate pretest and posttest counseling, particularly with regard to the stress/uncertainly associated with discovering variants of unknown significance (VUS).[8]

Prenatal WES has the potential to increase the ability to provide a more precise diagnosis, which will then improve the ability to counsel families. It is also often the first step in improving the path toward informed diagnosis and treatment, which is especially important in the era of advancing in utero fetal therapy. This article discusses the current literature regarding prenatal WES, clinical indications for WES, challenges with interpretation/counseling (VUS), research priorities, ethical issues, and potential future advances.

PRENATAL

As of July 2017, the prenatal data for exome sequencing currently includes 16 case series with 5 or more fetuses (7 articles and 9 conference abstracts) and several

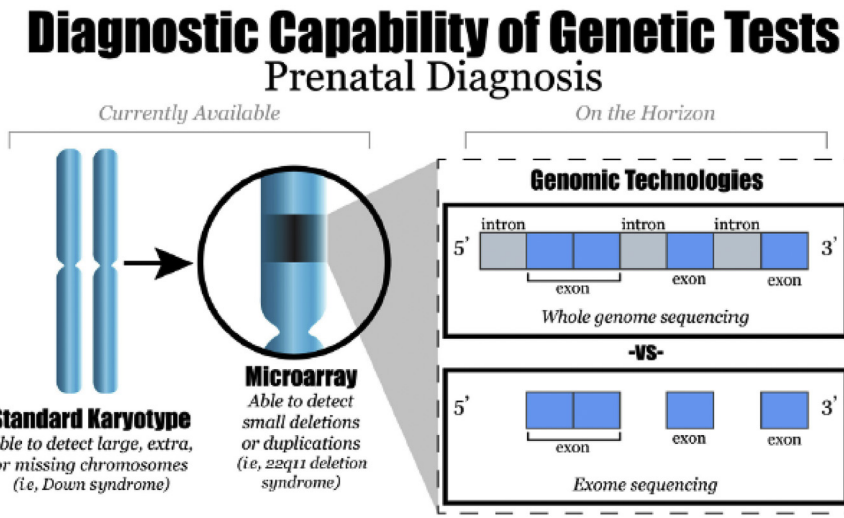

Fig. 1. New genomic technologies such as whole genome and whole exome sequencing have the ability to interrogate the fetal genome more comprehensively than currently available tests. (*From* Hardisty EE, Vora NL. Advances in genetic prenatal diagnosis and screening. Curr Opin Pediatr 2014;26(6):635; with permission.)