Whole genome sequencing of de novo balanced rearrangements in prenatal diagnosis

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Whole genome sequencing of the DNA code of three prenatal samples provided a detailed map of the locations of their chromosomal abnormalities in 14 days, scientists reported today at the American Society of Human Genetics (ASHG) 2012 meeting in San Francisco.

"Such a relatively brief timeframe will enable physicians to predict diagnosis of serious congenital disorders prenatally to counsel the parents and plan perinatal care of infants with chromosomal rearrangements," said Zehra Ordulu, M.D., Brigham and Women's Hospital and Harvard Medical School medical research fellow in obstetrics, gynecology and reproductive biology, who presented the study.

In the study, whole genome sequencing was used after current prenatal diagnostic methods of karyotyping and array comparative genomic hybridization (aCGH) to provide nucleotide level precision were conducted.

Karyotyping and aCGH studies of the prenatal samples provided the first clues of "balanced de novo chromosomal rearrangements," and prompted the investigation by genomic sequencing.

Clinical consequences of such chromosome rearrangements, which are defined as the relocation of chromosome segments without any loss or

gain in genomic material, are rare, not inherited and challenging to predict without knowledge of the precise breakpoints.

"Unlike karyotyping, aCGH and other standard methods, whole genome sequencing provided the information to detect the 'breakpoints" in the chromosomes at which the rearrangements occurred and thereby to determine the genomic regions altered," said Cynthia C. Morton, Ph.D., William Lambert Richardson Professor in obstetrics, gynecology and reproductive biology, professor of pathology at Brigham and Women's Hospital and Harvard Medical School and incoming president-elect of ASHG.

"Early detection of a genetic disorder is of significant importance for informing genetic counseling and for managing the pregnancy, birth and further clinical follow-up," said Dr. Morton, who headed the study.

"This study foretells an empowered prenatal diagnostic environment in which DNA sequencing becomes the standard of care," she added.

Dr. Ordulu also added, "Next-gen whole-genome sequencing in prenatal diagnosis for chromosomal rearrangements offers an unparalleled high resolution test for diagnosis and management of genetic disorders."

By using whole genome sequencing, Drs. Morton, Ordulu and collaborators determined in a third trimester prenatal sample of the first case that CHD7, a causal gene in CHARGE syndrome, was disrupted.

"Whole genome sequencing was consistent with a diagnosis of CHARGE syndrome, which was not possible based on prenatal imaging and the other commonly used prenatal genetic testing methods. This diagnosis would have changed medical care from an initial plan to repair an isolated heart defect to management of a morbid condition requiring immediate assessment of breathing and feeding difficulties," said Dr.

Ordulu.

In the second and third pregnancies, sequencing revealed a single disrupted gene. "Whole genome sequencing reassured the parents that a known genomic syndrome is not associated with the single disrupted gene and provided valuable additional information to the historical risk assessment of an untoward outcome," Dr. Ordulu said.

Provided by American Society of Human Genetics