WHEN SHOULD SINGLE GENE, GENE PANEL AND EXOME SEQUENCING BE APPLIED IN STRUCTURALLY ABNORMAL FETUSES?

INTRODUCTION

The advent of high-throughput Next-Generation Sequencing (NGS) has allowed to sequence the whole human genome in a single reaction. Our group initially applied the NGS technology to diagnose monogenic disorders, using single gene studies when a specific fetal anomaly pattern was attributed to a particular gene, or a gene panel if the fetal anomaly pattern was probably caused by several genes. Since 2016, when the observed fetal phenotype did not overlap with a previously described phenotype, we applied the “solo-clinical exome sequencing (CES)”, which entails sequencing the fetus alone, and interpreting the OMIM genes.

OBJECTIVE

To assess the diagnostic yield of different Next-Generation Sequencing (NGS) studies: single gene, gene panel or “solo” clinical exome sequencing (solo-CES), in fetuses with structural anomalies, normal chromosomal microarray analysis (CMA) in the absence of a known familial mutation.

RESULTS

During the study period (2015-2019), 118 NGS studies were performed in 108 structurally abnormal fetuses with a normal CMA. Overall diagnostic yield accounted for 35% (41/118) of samples and 38% (41/108) of the fetuses. Diagnostic yield in gene panels was 32% (12/37), similar to 39% (28/71) in solo-CES. Single gene NGS studies were abandoned in 2018 because of the observed low yield (10%: 1/10).

In specific fetal anomalies, a gene panel was preferred. “Gene panel” was defined as the test that analyzes by NGS multiple genes at once, ranging from 2 to 200 in our study, associated to a specific fetal phenotype; “solo-CES” was consistently offered in: a) Multisystem anomalies (at least 2 major anomalies from different anatomical systems); b) Recurrent anomalies (the same major anomaly in consecutive pregnancies); and c) Severe skeletal dysplasias with at least bilateral upper and/or lower limbs micromelia below-3 SD, not resembling osteogenesis imperfect.

During the last 17 months (July 2018- November 2019) of the study, pregnancies 115 affected by multisystem or recurrent structural fetal anomalies from 7 further 116 participating centers were also recruited and studied by means of CES.

Pathogenicity of variants identified in genes that were related to the index case phenotype or overlapping phenotypes was assessed following the American College of Medical Genetics and Genomics (ACMG) guidelines.

MATERIAL AND METHODS

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