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Editorial

Fetal Precision Medicine Achieved with Trio Exome Sequencing Analysis

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The topic of clinical decision-making as it relates to the selection of prenatal diagnostic tests is currently a subject of ongoing investigation within the academic community. Congenital anomalies, as defined by the World Health Organization (WHO), are structural or functional abnormalities that occur during intra-uterine life. They can be identified prenatally, at birth, or any time after birth. Moreover, they occur in approximately 2–3% of live births and 20% of spontaneously aborted fetuses [1]. Current guidelines recommend chromosomal microarray analysis (CMA) as a first-tier prenatal test for fetal anomalies [2]. Recent data has established next-generation sequencing (NGS) as the gold standard for detection of postnatal genetic diseases. NGS shows excellent diagnostic yield for invasive prenatal diagnosis (IPD) of fetal samples obtained through amniocentesis and CVS (Chorionic Villus Sampling) following negative CMA results [3]. Using whole-exome sequencing and trio analysis (mother, father and proband), Gabriel *et al*. [4] identified the genetic origin of fetal ultrasound abnormalities in 189 of 500 (37.8%) fetuses. In 89 cases (47.1% of the solved cases), the cause was a heterozygous *de novo* variant, thus showing the importance of trio exome sequencing for the identification of prenatal disease. Similar results were obtained by Corsten-Janssen *et al*. [5], who identified the genetic origin in 8 of 23 fetuses (35%) that showed ultrasound abnormalities. Despite the recent decrease in the number of births in Italy, it is estimated that approximately 10,000 children per year are suspected and/or recognized with genetic alterations. This means that genetics laboratories are under great pressure to develop comprehensive genetic tests based on sequencing exome analysis. Such tests are requested by pediatricians, neurologists, neuropsychiatrists, pediatric endocrinologists, geneticists and many other specialists seeking to identify the cause of a pathogenic phenotype. The most common genetic cause of congenital anomalies is a single-gene defect, responsible for around 17% of all congenital anomalies [6,7]. Chromosomal changes are identified in about 10% of children with congenital anomalies [7], while known environmental and maternal causes are responsible for a further 4–10% [7]. The latter group includes congenital anomalies believed to have environmental causes, or to be multifactorial. Multifactorial implies multiple, undefined gene variants that interact with environmental factors to cause a specific anomaly. It is important to note that fetal malformations diagnosed by ultrasound and once considered to be infectious, environmental, idiopathic or occasional, have since been verified as largely genetic in origin [8]. Such genetic causes are becoming more prevalent, and the number of malformations considered to be due to environmental or infectious causes is decreasing. A recent study of pediatric hospital admissions found that almost 70% of patients had a condition with a genetic contribution [9]. Importantly, children affected by a recognized genetic disease are in greater need of healthcare, showing in comparison to all other remaining patients (without genetic disease) poor outcomes 2.9% versus 7.6% respectively [10,11]. This means that genomics technologies like exome sequencing offer a promising strategy for fetal precision medicine [12]. Modern technologies allow genetic tests to be carried out in a very short time and at increasingly low costs. Recently, the implementation of invasive prenatal diagnosis (IPD) by exome sequencing and based on trio analysis (analysis of genetic data from the foetus and its two parents) has shown high diagnostic yields [4,13]. Despite the notable risk of miscarriage, it is now thought that pregnant women who undergo amniocentesis face the same risks as women who do not undergo this procedure, or even lower with the use of specific prophylaxis [14–18]. In conclusion, trio analysis involves exome sequencing performed on the amniotic fluid (or chorionic villi) and on both parents. It is used to evaluate pathogenic mutations after negative CMA results, and should markedly improve diagnostic yield in the emerging field of fetal precision medicine [12]. However, some challenges must be overcome before exome sequencing can be used routinely in prenatal diagnosis. These include the interpretation of variants in partial phenotypes based mostly on ultrasound, X-ray and/or magnetic resonance imaging, as well as the constraints of turnaround time inherent to the ongoing pregnancy. Nevertheless, it is imperative for healthcare specialists to have comprehensive knowledge of the current advances in prenatal techniques. The importance of providing adequate information to parents should also not be underestimated, as they have a right to be fully informed and to make autonomous decisions in terms of prenatal care [19].

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Conflict of Interest

The authors declare no conflict of interest.

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