S11 - Identifying the Genetic Causes Underlying Prenatally-diagnosed Structural Congenital Anomalies (SCAs) by Whole-exome Sequencing (WES)

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Introduction: Whole-exome sequencing (WES) has become an invaluable tool for genetic diagnosis in Paediatrics. However, it had not been widely adopted in the prenatal setting at the time of this study. We evaluated the use of WES in prenatal genetic diagnosis in fetuses with structural congenital anomalies (SCAs) detected on prenatal ultrasound.

Methods: Thirty-three families with fetal SCAs on prenatal ultrasonography and normal chromosomal microarray results were recruited. Genomic DNA was extracted from various fetal samples including amniotic fluid, chorionic villi, and placental tissue. Parental DNA was extracted from peripheral blood when available. We used WES to sequence the coding regions of parental-fetal trios and to identify the causal variants based on the ultrasonographic features of the fetus.

Results: Pathogenic mutations were identified in three families (n=3/33, 9.1%), including mutations in *DNAH11*, *RAF1* and *CHD7*, which were associated with primary ciliary dyskinesia, Noonan syndrome, and CHARGE syndrome, respectively. In addition, variants of unknown significance (VUSs) were detected in six families (18.2%), in which genetic changes only partly explained prenatal features.

Conclusions and Discussion: WES identified pathogenic mutations in 9.1% of fetuses with SCAs and normal chromosomal microarray results. Our diagnostic yield is comparable to the PAGE (Prenatal exome sequencing analysis in fetal structural anomalies detected by ultrasonography) study (Lord et al. Lancet 2019). WES facilitates genetic diagnosis of SCAs, which in turn enables more accurate prediction of prognosis and recurrence in subsequent pregnancies. However, the Joint Position Statement from the International Society for Prenatal Diagnosis, the Society for Maternal Fetal Medicine and the Perinatal Quality Foundation does not support its routine use as a diagnostic test due to insufficient validation data and knowledge about its benefits and pitfalls. Currently it is ideally done in the setting of a research protocol. Databases for fetal genotype-phenotype correlations and standardized guidelines for variant interpretation in prenatal diagnosis need to be established to facilitate the routine use of WES in prenatal diagnosis.

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