Re-analysis of Exome Sequencing Data of Prenatal Cases Presenting with Fetal Structural Anomalies

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Introduction

Rapid exome sequencing for fetuses with structural anomalies detected on ultrasound has been implemented into clinical practice in the UK Genomics Medicine Service, following a series of studies demonstrating diagnostic rates between 6.2% - 80% in cases previously undiagnosed by other techniques. Prenatal diagnosis is increasingly shown to provide information for prenatal, perinatal and postnatal management and treatment (Best *et al.* 2018), in addition to facilitating accurate assessment of recurrence in future pregnancies.

Reanalysis of exome data of previously unsolved cases in the postnatal setting has been shown to further increase the diagnostic yield by approximately 12% (Ji *et al.* 2021).

Objectives

To evaluate the diagnostic potential of exome sequence reanalysis in previously unsolved fetal anomaly cases and identify contributing factors to diagnosis.

Methods

Cases of fetal anomalies detected on US were referred to Clinical Genetics at St George's Hospital, London. Fetal DNA was extracted from CVS, amniotic fluid, fetal blood or post-mortem fetal tissue. Maternal cell contamination was examined where relevant. DNA was enriched using Agilent SureSelect Clinical Research Exome V2 (CRE V2) or Nonacus ExomeCG and sequenced on Illumina NextSeq 500 or NovaSeq. Secondary and tertiary analysis of DNA sequences and review of SNVs and CNVs was undertaken using the Congenica clinical decision platform. Analysis of CNVs was performed only on DNA samples enriched with Nonacus ExomeCG. Re-analysis was performed 6 - 48 months after initial interpretation, using 1) updated fetal anomaly gene panels and if still negative 2) gene agnostic prioritisation.

Results and Conclusion

Through original exome sequencing analysis, a diagnosis was achieved in 59/180 fetuses (33%). Of 82 cases assessed for CNVs, 2 had pathogenic variants (2.4%). Re-analysis was performed on 123 unsolved cases, including cases with pathogenic CNVs only. Updated figures will presented.

This study illustrates the diagnostic utility of re-analysing exome sequencing data in previously unsolved prenatal cases with fetal structural anomalies detected by USS.