

Diagnosis of fetal structural abnormalities using whole exome sequencing

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Objective

To molecularly diagnose cases of unexplained fetal anomaly using whole exome sequencing, with phenotype derived from ultrasound, family history and/or post mortem investigation.

Methods

Patients with a fetal abnormality detected on ultrasound were referred to clinical genetics at St George's Hospital, London. Fetal DNA was from CVS, amniotic fluid, fetal blood or tissue. Maternal cell exclusion was performed where relevant. Familial samples were sequenced where possible. DNA was enriched using Agilent SureSelect CREv2 and sequenced using Illumina NextSeq 500. Variant analysis performed using Sapienita™.

Results

Of 55 families referred to date, exome sequencing identified diagnosis in 22 cases (40%) involving one each of, FGFR2, LZTR1, NIPBL, PTPN11, RAF1, RMRP, SLC26A2, TSC1, UBE2A, CHD7, PIEZO1, POMGNT1, SLC6A9, TUBA1A, FAM111A, PAFAH1B1, EVC2, FOXC1, SLC17A5, KCNJ2 and KMT2D. DNA to primary report has been in as little as 5 working days. Findings of particular note include atypical skeletal presentation of RMRP mutations and inter-family variability of a UBE2A mutation. A KMT2D mutation was identified in a case with multisystem abnormalities.

Conclusion

Diagnostic rate in this selected case series is higher than published unselected cohorts. Molecular diagnosis was not always the primary clinical diagnosis highlighting both the challenge of reduced phenotype detail in this population and the importance of expanding prenatal genotype-phenotype correlations. Positive diagnostic rate was higher in cases with fetal oedema/hydrops. There is increasing evidence of the role of KMT2D as a cause of fetal anomalies.