

Diagnosis of fetal abnormalities using exome sequencing: translating research into practice

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Structural anomalies are detected on ultrasound in around 3% of pregnancies and are responsible for approximately 20% of perinatal deaths (1). Following standard genetic testing (karyotyping and

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chromosomal microarray) the majority of cases remain unexplained. We undertook prenatal exome sequencing (ES) of forty-two fetuses with structural anomaly. This approach included sequencing >22,000 genes, and analysis with phenotype specific 'virtual gene panels' (see supplementary material). The majority of these cases were ongoing pregnancies or those at the point of termination. Some cases were undertaken after post-mortem examination. The majority (40%) were affected by multisystem abnormalities. A molecular diagnosis was made in 38% (16/42) of cases, higher than in recently published series of unselected fetuses with structural anomalies which had 8.5% and 10% respectively (2,3) (supplementary results, supplementary table 1). 44% (6/16) of molecular diagnosis were not the suspected clinical diagnosis, emphasising the continued importance of expanding prenatal genotype-phenotype associations.

Although small numbers, the highest diagnostic rate was in fetuses with a skeletal phenotype (2/3; 67%), followed by Non Immune Fetal Hydrops (3/5; 60%). In total, 15 cases had hydrops or abnormal fluid collections in a single extravascular fetal compartment, either with or without other abnormalities. The diagnostic rate in this group was 54% (8/15), which was higher than in those without abnormal fluid redistribution (26% 7/27).

One of the particular challenges of molecular prenatal diagnosis is limited phenotype information, due to the limited resolution of antenatal ultrasound and the unknown presentation of many known genetic conditions in-utero. Case 10 presented on ultrasound with increased nuchal translucency and small cystic hygroma and holoprosencephaly (supp. figure 1). Deep phenotyping on post-mortem revealed multiple abnormalities; ES identified a likely pathogenic variant in *KMT2D* (NM_003482.3:c.2347_2350delCCTG; p.Pro783Argfs*146), a gene associated with Kabuki syndrome, a postnatally recognised condition which has characteristic facial features. However increasing evidence suggested *KMT2D* is a cause of fetal anomalies. In an unselected cohort of fetuses with ultrasound detected anomalies, this was found to be the most frequently mutated gene (2).

The dialogue between maternal-fetal medicine specialist and geneticist would be facilitated by the real-time electronic integration of ultrasound findings into genomic records. In cases where a negative ES was reported during an ongoing pregnancy, variants were reinterpreted in the context of additional postnatal or post-mortem phenotyping. Additional diagnosis after the conclusion of the pregnancy may provide management relevant information to the child and/ or useful information to the family about recurrence risks. Genetic services need capacity to routinely re-interrogate genomic data in the

light of rapidly progressing knowledge about prenatal phenotypes, genomic variants and gene discovery.

With prenatal ES soon to be routinely available via the new genomic testing directory for England, our findings help to inform clinical implementation of this new technology.

Accepted Article

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