Unblurring the ultrasound lines: 45% of infants with prenatal findings receive a reportable result on diagnostic exome sequencing

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The utility of diagnostic exome sequencing (DES) in neonates has been well established; however, prenatal DES use remains limited. Studies on prenatal DES have reported a wide range of diagnostic rates and are primarily focused on fetal structural anomalies. Here, we looked at prenatal histories of infants who underwent DES at one commercial laboratory to assess pregnancy data including non-fetal ultrasound findings.

Clinical and genetic testing histories were reviewed for patients ≤4 months referred for DES. Prenatal imaging and previous testing were categorized by type of study, result and time of testing (prenatal or postnatal). Prenatal findings were tabulated as (1)fetal anomalies, (2)non-fetal anomalies (ie. umbilical cord problems, poly/oligohydramnios, or placental abnormalities) and (3)fetal edema, which ranged from increased nuchal translucency to hydrops.

Of the 349 cases reviewed, 37.5% (131/349) had no reported abnormal findings during pregnancy. At least one prenatal finding was seen in 197 (56.5%) cases, and the remaining 21 cases had insufficient records to determine initial detection time. The overall diagnostic rate was 29.8% (104/349) with an additional 38 cases (10.9%) receiving an uncertain report due to a VUS or uncertain clinical overlap between the patient's phenotype and the reported gene. Cases with prenatal findings had a higher (not significant) diagnostic rate compared to those with postnatal diagnoses (33.0% v. 28.2%). Factoring in uncertain findings, this number increased to 45.2% (89/197) for prenatal-onset cases. This is higher than the postnatal group, in which 35.9% (47/131) of cases had reportable findings (p=0.09). Severity of fetal edema did not correlate to higher diagnostic rates. Infants with disorders involving the genitourinary (77.0%), renal (73.0%) and musculoskeletal (69.0%) systems were most likely to have an abnormal prenatal finding. Age at time of testing, positive family history and availability of family samples for trio analysis did not significantly impact diagnostic rate.

Cases with abnormal pregnancy findings other than fetal structural anomalies (n=54) included the following: 30 with fetal growth abnormalities, 25 with non-fetal anomalies, mostly comprised of abnormal fluid levels and 11 with decreased/abnormal fetal movements. The diagnostic rate in this group was 48.2% (26/54), which is significantly higher than the rate for cases with a fetal structural anomaly reported (26.6% (37/139); p=0.004), suggesting that prenatal DES, even in the absence of fetal anomalies is a valuable diagnostic tool.