The added yield of whole exome sequencing in fetuses with suspected central nervous system abnormalities

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Objective
In cases of suspected fetal central nervous system (CNS) abnormalities, it is standard practice to perform prenatal chromosomal microarray (CMA). This however, has an added diagnostic yield of only 5-7% over standard karyotype. Thus the underlining cause remains unknown in most cases because many of these conditions are due to single gene mutations that cannot be detected by CMA. Because such mutations may occur in a large number of potential genes, it is impractical to perform gene-specific sequencing in most cases. The purpose of this study was to assess the added value of whole exome sequencing (WES) in fetuses with CNS abnormalities following a normal CMA result.

Methods
Fetuses with CNS abnormalities whose CMA results were negative were offered WES. During the study period (2014-2016) 7 cases of CNS anomalies detected prenatally (total of 9 fetuses) were evaluated by WES following normal CMA and all except one case were done in parallel with parental samples (trio).

Results
A pathogenic or likely pathogenic variant was reported in 4 cases including a de novo COL1A1 mutation in a female fetus, with several anomalies including short long bones, malformed vertebras, enlarged and hyperechoic kidneys and abnormal lateral ventricular walls and early sulcation; a previously described homozygous VRK1 mutation in a fetus with sonographic findings of abnormal sulcation, flatten sylvian fissure and an underdeveloped parieto-occipital fossa; an X-linked ARX mutation in a fetus with several brain abnormalities including agenesis of corpus callosum, heterotopia and a 5*10 mm interhemispheric cyst; and 2 affected fetuses (bilateral clubfoot and absence of fetal movements) of the same couple with compound heterozygote variants in the SCN4A gene. In addition, a pathogenic gene deletion and a variant of uncertain significance (VUS) of the NPHP1 gene were detected in 2 fetuses with multiple periventricular pseudocysts (PVPCs) of the same couple. Two additional cases (a recurrent Dandy-Walker malformation and a case of macrocephaly with aberrant right subclavian artery) had normal WES results.

Conclusion
Whole exome sequencing dramatically improves prenatal diagnosis in euploid fetuses with normal CMA but with structural abnormalities involving the CNS.