Does deep phenotyping combined with prenatal exome sequencing for fetal brain abnormalities increase diagnostic yield?

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Background

- Congenital anomalies affect 2-4% of all infants and are responsible for 20% of perinatal deaths.
- In the setting of prenatally diagnosed congenital anomalies, where standard genetic testing including microarray are negative, ES has been shown to improve diagnostic yield
- Accurate interpretation of ES results is heavily reliant upon available prenatal phenotypic information, which is often limited to ultrasound findings

Objectives

To evaluate whether deep prenatal phenotyping of fetal brain abnormalities (FBA) increases diagnostic yield of trio-exome sequencing (ES) compared to standard prenatal phenotyping.

Methods

Prospective multi-center prenatal exome sequencing study.

Inclusion criteria:

- Fetal brain abnormality diagnosed on prenatal ultrasound
- Normal fetal karyotype and microarray
- Fetal and parental DNA available

Primary Outcome:

Cases with diagnostic ES results were compared to those with non-diagnostic results by standard versus deep prenatal phenotyping.

- *Standard phenotyping:* phenotype based on targeted ultrasound alone
- *Deep phenotyping:* phenotype based on fetal MRI, autopsy (when available), and/or known phenotypes of other affected family members.

Analysis: Data were analyzed using t-test, chi-square and pairwise comparisons as appropriate with $p<0.05$ considered significant.

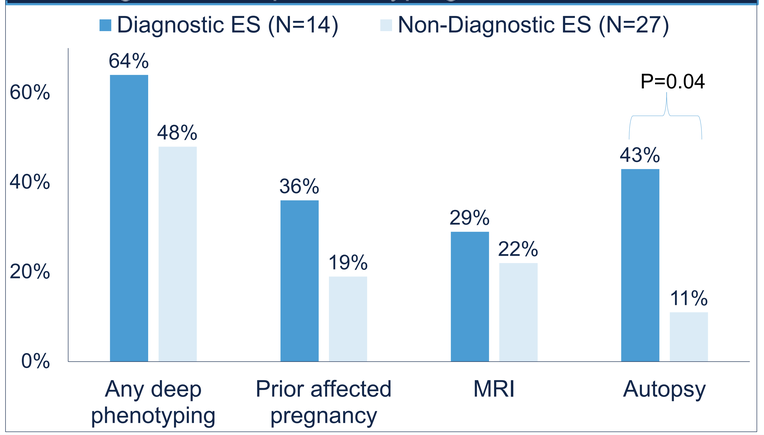
Results

Table 1. Maternal Demographics

	N=41
Age (mean, SD)	29 4.1
Caucasian Race	35 (85)
Employed	25 (61)
Married	32 (78)
College Education	32 (78)
Prior Genetic Testing	23 (56)
Prior Affected Pregnancy	10 (24)

Data shown as n (%)

Figure 1. Deep Phenotyping and ES Results



Results

Table 3. Bivariable Analysis of FBA type and ES Results

	Diagnostic ES (N=14)	Non-Diagnostic ES (N=27)	P-value
Cavum septum pellucidum anomalies	2 (14)	6 (22)	0.54
Posterior Fossa Anomalies	7 (50)	9 (33)	0.3
Ventriculomegaly	4 (29)	7 (25)	0.9
Absence of Corpus Callosum	1 (7)	7 (25)	0.15
Hydranencephaly/ Hydrocephalus	1 (7)	4 (15)	0.5
Anencephaly/ Encephalocele	0	4 (15)	0.13
Holoprosencephaly Spectrum	1 (7)	1 (3)	0.63
Open Neural Tube Defect	0	1(3)	0.5

Data shown as n (%)

Conclusions

- Additional phenotypic information, particularly autopsy, may increase diagnostic yield of prenatal ES for FBA.
- This highlights the need to identify specific prenatal phenotypic variables that may increase diagnostic yield in the context of sequencing efforts.