Clinical diagnostic exome sequencing identified compound heterozygous *ASPM* gene alterations in a fetus with marked microcephaly.

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Abstract:
Diagnostic exome sequencing (DES) has been shown to be a successful option for diagnosing individuals with previously uncharacterized genetic conditions, and has recently become a clinical option available for pregnancies with prenatally detected ultrasound anomalies. We report a postmortem case referred to our laboratory for DES due to marked microcephaly that was identified by ultrasound during the third trimester of pregnancy. Additional prenatal history includes an abnormal PAPP-A level identified by first trimester screening and an abnormal fetal MRI. Karyotyping and microarray were normal. Autopsy of the female fetus identified microcephaly with dysmorphic features including sloping forehead, broad nasal bridge, hypertelorism, arched eyebrows, and slight down slanting palpebral fissures. Neuropathology revealed frontal pachygyria, small cranial vault, flattening of the anterior cranial fossa, flat occiput, small brain, markedly depleted cortical neurons and white matter, hypoplasia of the olfactory bulbs and corpus callosum, and head circumference <3%ile. There was no reported family history of similar findings. DES was performed on a fetal DNA sample in addition to parental blood samples, whose results were used during variant filtering and analysis. Results revealed compound heterozygous *ASPM* alterations in the fetal sample, including one maternal c.1386C>G (p.Y462*) nonsense mutation and one paternal c.8988-1G>C splice site mutation. The *ASPM* gene encodes the abnormal spindle-like microcephaly-associated protein. Alterations in this gene are generally inherited in an autosomal recessive fashion in association with primary microcephaly-5 (MCPH5), a condition characterized by decreased occipital-frontal circumference present at birth and associated with mental retardation and speech delay. Other features may include seizures and/or short stature. Brain MRI results typically observed in MCPH5 are variable, with findings including simplified gyral pattern, enlarged ventricles, partial agenesis of the corpus callosum, mild cerebellar hypoplasia, focal cortical dysplasia, and unilateral polymicrogyria. Collectively, the evidence supports that the *ASPM* alterations are the cause of the clinical findings in this fetus and that the parents have a 25% risk for future affected pregnancies, information that could not be accurately concluded based on ultrasound findings alone. Additionally, this case illustrates the importance of discussing the option of collecting and maintaining DNA samples following pregnancy termination, fetal demise, or perinatal death in pregnancies affected with multiple congenital anomalies and/or a suspected genetic condition. Pathogenic DES results allow for recurrence risk counseling and provide the option for targeted prenatal diagnosis in future pregnancies.

Abstract Review Categories:
Perinatal Genetics
Molecular Genomics/Exome

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Prenatal diagnosis
Genetic testing
Mutation detection
Inheritance patterns
Congenital anomaly
Malformation
Genotype-phenotype correlations
Counseling
Ultrasound
Next Gen sequencing

Learning Objectives:

1. To describe the specific ultrasound and postmortem findings reported in a fetal case that obtained a diagnosis following positive DES results.
2. To outline the details of the positive gene and alterations identified in a case sent to our laboratory for diagnostic exome sequencing.
3. To recommend that providers discuss the option of collecting and maintaining DNA samples following cases of pregnancy termination, fetal demise, or perinatal death in pregnancies affected with multiple congenital anomalies and/or a suspected genetic condition.
4. To point out that diagnostic exome sequencing results may be helpful in the counseling of families who wish to determine recurrence risks for future pregnancies and for future generations.