Genetic diagnosis of severe fetal akinesia syndrome by means of whole exome sequencing

Reischer T, Liebmann-Reindl S, Balendran S, Streubel B
Medical university of vienna, Vienna, Austria

Objective
The term fetal akinesia represents disorders within a broad spectrum of diseases leading to reduced or absent fetal movements. This clinical entity is often recognized as a sequence of related deformational changes and includes features like intrauterine growth restriction, craniofacial anomalies, limb contractures, together with pregnancy complications such as polyhydramnios. In the last years, gene discovery was revolutionized by implementation of NGS technologies, whereas research mainly focused on postnatally well-defined phenotypes and less on fetal lethal disorders. Herein we present our case series where we used whole genome sequencing to diagnose severe fetal akinesia syndrome.

Methods
We included 15 affected fetuses in 11 families. Fetal akinesia syndrome was diagnosed prenatally by ultrasound and/or MRI. In the majority of cases the clinical diagnosis led to the decision of termination of pregnancy or later resulted in perinatal death. In all cases chromosomal aberrations were excluded. Exome sequencing was performed in the index case of each family.

Results
In 4/11 families, including two consanguineous families, more than one fetus was affected and an autosomal recessive disorder was likely. We correlated exome data with 33 known disease-related genes and found pathogenic variants of CNTN1-gene, RYR1-gene, NEB-gene and GLDN-gene respectively in six cases of four families. In two other cases exome sequencing revealed a disease causing variant in the HRAS-gene and the TNNT3 –gene. In one case exome sequencing was negative, but a DMPK-gene repeat expansion was identified. In the remaining six cases no disease causing variant could be identified.

Conclusion
Fetal akinesia syndrome is a genetically heterogeneous disorder, following different types of inheritance. In this case series in 40% (6/15) a variant in a known disease-related gene was found. In summary, exome sequencing lead to a diagnosis in 55% (6/11) of these families. Still, in a large part the underlying genetic cause remained unknown, whereas precise clinical evaluation in combination with exome sequencing shows to be the most important tool to identify the disease-causing variant.