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Prenatal molecular diagnosis of heterotaxy syndromes: the emerging role of exome sequencing

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Background and Objectives

Vertebrate morphogenesis occurs along three orthogonal axes (anteroposterior, dorsoventral and left-right).

Anteroposterior and dorsoventral defects usually result in conditions so severe that they are incompatible with life.

Laterality defects include a broad spectrum of morphological anomalies with impaired induction of left-right asymmetry.

Heterotaxy Syndrome is characterized by a different arrangement of major organs. A segmental approach allows to classify the side defects found on ultrasound.

We describe the results of prenatal exome sequencing performed on fetuses with heterotaxy, which turned out to be caused by **variants in genes involved in the functioning of ciliary complex** in all cases.

Materials and Methods

Since 2019, we recruited 5 fetuses diagnosed with heterotaxy through **fetal echocardiography**.

4 → amniocentesis

- **3 cases**, with **normal karyotype and chromosomal microarray**, underwent **Prenatal Exome Sequencing**, performed in trio on genomic DNA from amniotic fluid with turn-around time during the pregnancy and parental leukocytes.
- in 1 case genetic tests could not be carried out due to cell culture failure

Targeted enrichment was attained using the Twist Custom Panel Kit. The library was sequenced on an Illumina NovaSeq6000 platform. Fastq files were aligned to the human reference GRCh37/hg19. BWA Enrichment application of BaseSpace (Illumina) and TGex software (LifeMap Sciences) were used for variant calling and annotation. Sequence data were analyzed, candidate variants were checked in databases. Sanger validation was performed on fetal DNA and parents.

Results

Case 1 → azygos continuation of the inferior vena cava and abdominal situs inversus.

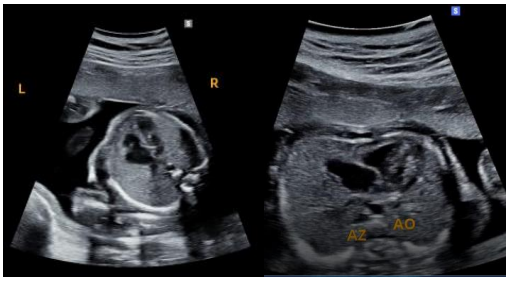
Prenatal Exome Sequencing: c.737_740delAGGC (p.Gln246fsTer4) and the c.1282G>T (p.Glu428Ter) variants in compound heterozygosis in ***CFAP53*** (NM_145020.4).

Case 2 → right atrial isomerism, atrioventricular canal with single right ventricle, pulmonary valve atresia and dextroposed stomach.

Prenatal Exome Sequencing: c.2507_2508delAA (p.Lys836SerfsTer3) and the c.414G>A (p.Trp138Ter) variants in compound heterozygosis in ***CCDC39*** (NM_181426).

Case 3 → right atrial isomerism, atrioventricular canal, transposition of great arteries and total pulmonary venous return in superior vena cava.

Prenatal Exome Sequencing: c.8683C>T (p.Leu2895Phe) variant in ***DNAH9*** (NM_001372.3).



Conclusions

Fetuses diagnosed with laterality defect are suitable candidates for exome sequencing due to the emerging high diagnostic rate of this group of morphological anomalies, which usually recognize an autosomal recessive inheritance.

A timely molecular diagnosis plays a fundamental role in genetic counseling, regarding ongoing pregnancy and recurrence risks, and in preventing any respiratory complications due to ciliary dyskinesias.

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