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Single Gene Disorders of the Human Fetus
resulting in fetal and neonatal loss

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Background

To date a total number of around **7,000 phenotypes** with a known molecular basis have been associated with **Mendelian inheritance**, identified as **monogenic (single-gene) or oligogenic disorders** (**MODs**), the vast majority being considered as **rare diseases**.

The exact or approximate number of MODs that become manifest in utero or perinatally is still unknown.

Current knowledge on the **fetal phenotype** of MODs, with **phenotype-genotype correlations**, is very **limited**.

Aim

This research focuses on
the **precision diagnosis** of **non-chromosomal genetic syndromes,**
which cause **congenital malformations and other birth defects**,
resulting in **fetal** or **neonatal death**.

Technology used: **Whole Exome Sequencing (WES)**

In various published prenatal WES studies, the diagnostic rates vary between 6.2% and 80%.

20 postnatal cases were selected as **phenotypes with suspected gene disorders/MODs,** based on the **pathological**, **histological** and **radiographical** findings provided by **expert perinatal autopsy with full postmortem examination**, combined with the **prenatal ultrasonographical findings**.

Chromosomal imbalances had been previously ruled out.

Fetal/neonatal DNA samples were extracted from tissues obtained at autopsy with written parental consent, following:

- **termination of pregnancy** (**TOP**) due to abnormal prenatal U/S findings (x12)
- **intrauterine fetal demise** (**IUFD**) (x2) with suspected gene disorder
- or **neonatal death** (**NND**) (x6) with suspected gene disorder

Results

A precision genetic diagnosis was established in 12/20 cases (60%).

Pathogenic or likely pathogenic variants (3 novel) were identified in **13** different genes, including **4 heterozygous** autosomal dominant, **3 homozygous** autosomal recessive, **2 compound heterozygous** autosomal recessive, and **4 X-linked**.

Pathogenic/likely pathogenic variants were identified:
in **9/14 (64%)** cases of TOP and IUFD (**fetal loss**) with multiple or isolated defects
and in **3/6 (50%)** cases of NND (**neonatal death**) with suspected metabolic, neuromuscular or neurodegenerative syndromes.

Variants of Unknown Significance (VUS) were very close to being likely pathogenic, with relation to the phenotype, **in 3/20 (15%)** cases.

Negative findings could be attributed to:
- a non-genetic sporadic occurrence of fetal malformations
- a different type of genetic defect
- a yet unknown pathogenic DNA variant
- technical limitations of the performed analysis

Conclusions

- "Molecular autopsy" can reach a significant diagnostic yield for fetal and perinatal MODs in selected cases with a relevant phenotype.
- "**Rare genetic syndromes" leading to fetal and neonatal loss are common as a group**, and may manifest with atypical phenotypes.
- Novel pathogenic or likely-pathogenic DNA variants are identified and Variants of Unknown Significance (VUS) can change to pathogenic, when correlated with a complete phenotype and functional studies.

Future Perspectives

➢Given the practical, social and economic limitations of NGS techniques, a large-scale **prospective multicenter study on a national level** is warranted, implementing molecular autopsy with NGS techniques in selected cases, as a significant tool in the identification and investigation of **gene disorders leading to malformation syndromes and perinatal loss or infant death in Greece.**

➢Potential association with DNA sequencing technology for the creation of gene panels for prenatal and postnatal clinical diagnostics.

References

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