Valuable insights after one year whole exome sequencing in a fetal/prenatal setting

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INTRODUCTION

Whole exome sequencing (WES) in a postnatal context has become a routine procedure in most genetic labs. Currently, the potential of WES in prenatal and fetal context is getting more explored.

The aim of this study is to evaluate the implementation of WES for fetuses with congenital anomalies and a normal copy number variant (CNV) result in a diagnostic workflow. Here, we present our results and insights after one year of exome sequencing in fetal/prenatal context.

KEEP IN MINDS

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METHODOLOGY

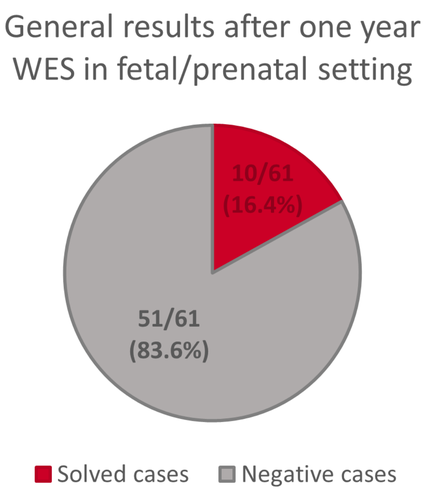
- Implementation of a **FAST-WES** track for prenatal testing and other defined urgent indications, with a maximal turn-around-time of 8 weeks.
- **Two different approaches** were distinguished: ongoing, and terminated pregnancies or miscarriages, further referred to as **prenatal and fetal**, respectively.
- Depending on the fetus's abnormalities, a **targeted gene panel or Mendeliome analysis** was performed *in-silico*, the latter comprising all human disease-linked genes.
- The **variant analysis strategy was optimized** to efficiently identify the causal variant, by focusing on *de novo*, X-linked or biallelic inheritance.
- **National Belgian guidelines (BeSHG)** have been established to standardize the testing and reporting strategy.

RESULTS

Overall results after one year

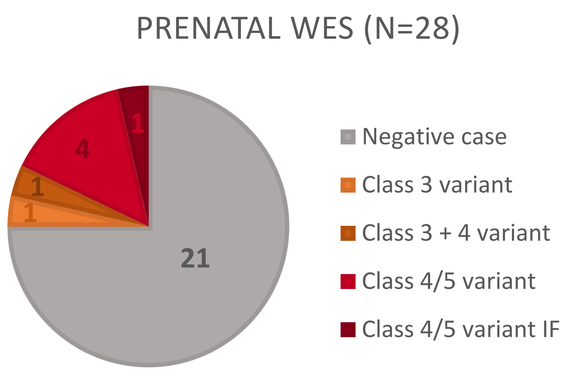
Over the period of one year, 61 structurally abnormal fetuses with normal copy number variant (CNV) analysis were investigated via exome sequencing.

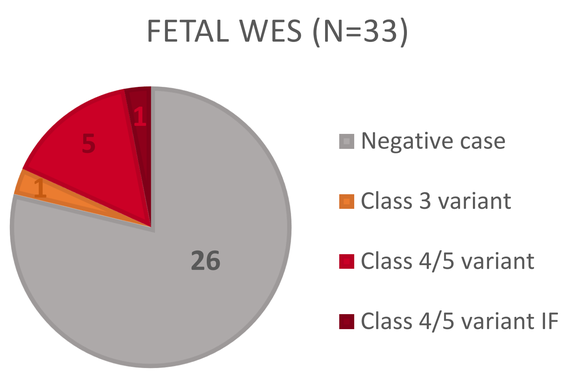
The overall diagnostic yield was 16.4%; in 10 out of 61 fetuses, a class 4 or 5 variant could be identified in the following genes: *AARS2, ASCC1, CDK10, COL1A1, COL2A1, COL5A1, EBP, FOXP3, GPC3 and TTN*.



Prenatal versus fetal context

When comparing analysis in prenatal versus fetal context, diagnostic yield was 17.9% (5/28) and 15.2% (5/33) respectively.





Among the prenatal analyses we found one *CDKN1C* variant, classified as a class 3 variant. Segregation was performed, leading to the reclassification of the variant as a class 2. The second class 3 variant was found in compound heterozygous state with another class 4 variant in *CDK10*. Furthermore, one inherited pathogenic incidental finding was reported in *BRIP1*.

For the fetal cases, in one fetus two hemizygous class 3 variants were identified, one in *HUWE1* and the other in *KIF4A*. The latter was found in the healthy brother after segregation and became a class 2 variant. Additionally, one pathogenic incidental finding was reported in *APOB*.

CONCLUSION

A **causal variant** could be identified as the underlying cause in **16.4% of fetuses with congenital anomalies** and a normal CNV result, confirming the added value of exome analysis in a fetal setting.

These results proof an **important contribution of WES within prenatal and fetal context** to obtain a higher number of molecular diagnoses and can broaden the understanding of aberrant fetal phenotypes and their underlying genetic cause.

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Targeted panel versus Mendeliome analysis

Diagnostic yield for targeted gene panels was 13% (3/23), which is less compared to 18.4% (7/38) for Mendeliome analysis.

Added value of ExomeDepth

Additional ExomeDepth analysis on the WES data revealed a small intragenic *ASCC1* homozygous deletion in a fetal case with heterozygous carrier parents. The deletion was confirmed via qPCR.