

EP 07.18 Congenital CNS malformations, yield of Whole Genome Sequencing as a primary diagnostic test

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- **Objectives**

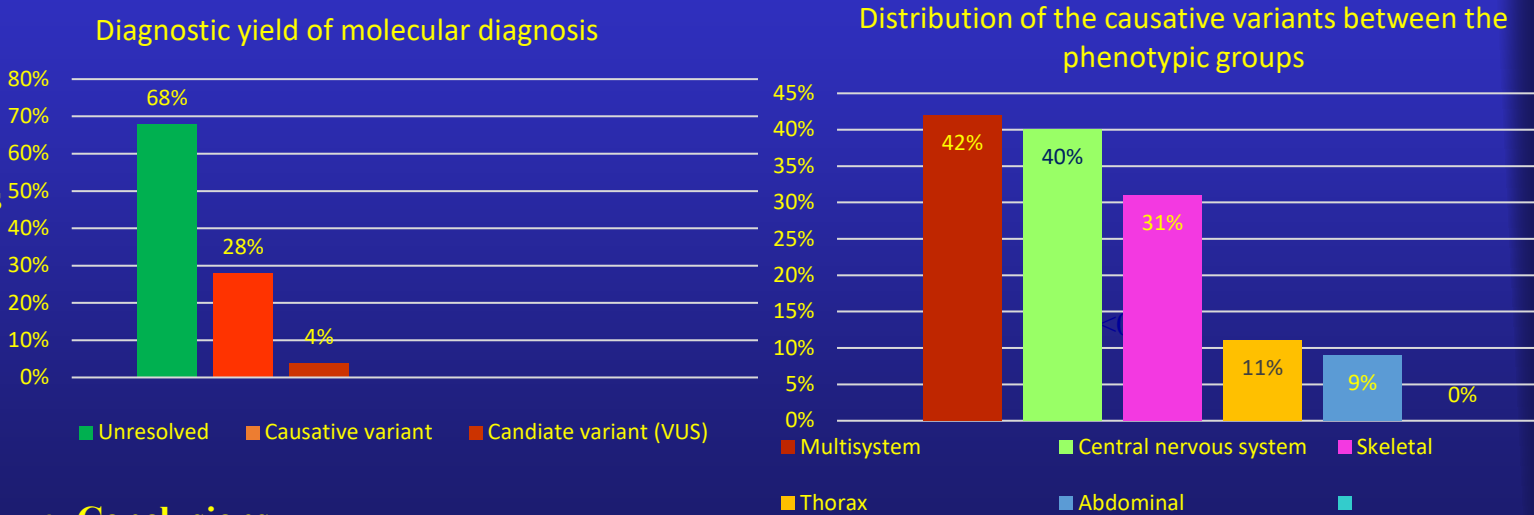
Investigation of the diagnostic yield of whole genome sequencing (WGS) in prenatally detected CNS malformations

- **Results**

A molecular diagnosis was achieved in 28/100 (28%) of cases. The diagnostic yield of the six different phenotypic groups were: multisystem 11/26 (42%), CNS 10/25 (40%), skeletal 4/13 (31%), thorax 2/19 (11%), abdominal 1/11 (9%) and other isolated anomalies 0/6 (0%). There were also 4 additional cases (4%) that carried variants considered potentially clinically relevant (VUS). In the 25 cases with CNS anomalies, causative variants were identified in 9 genes: COL4A1, FLVCR2, POMGNT1, PDHA1, FBXO11, CDH2, OFD1, SMARCC1 and L1CAM (n=2).

- **Methods**

Prospective study where 100 pregnancies with fetuses having different congenital malformations, negative for trisomies and causative copy number variants (CNVs), were further analyzed with fetal- parental trio WGS analysis. The phenotypes of the cases were divided into six different groups: multisystem (n=26), central nervous system (CNS) (n=25), skeletal (n=13), thorax (n=19), abdominal (n=11) and other isolated anomalies (n=6).



- **Conclusions**

WGS is an effective test in the investigation of prenatally detected malformations. A molecular diagnosis was found in 28% of all cases and in 40% of CNS malformations when chromosome aberrations already had been excluded. As these are a well-known cause of fetal anomalies, future studies using WGS as a primary diagnostic test including assessment of chromosome aberrations will most likely have a major impact on counselling the parents concerning prognosis and management of the ongoing pregnancy as well as provide estimates of recurrence risks and options in future pregnancies. Turnaround time and costs will need to decrease before WGS can be implemented as a primary diagnostic test in larger settings.