Prenatal exome sequencing (WES). A retrospective cohort study in fetuses with congenital defects detected by antenatal ultrasound.

CoGEN
Preconception, Preimplantation and Prenatal Genetic Diagnosis (CoGEN)

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INTRODUCTION

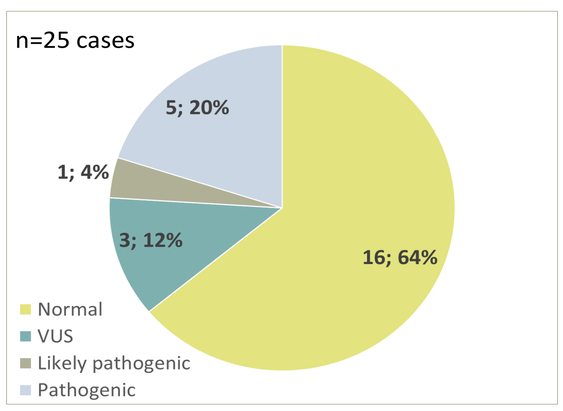
Whole exome sequencing (WES) is a diagnostic tool in postnatal settings for individuals with a suspected genetic condition. In prenatal settings, WES diagnostic yield ranges from 15% to 35%. The aim is to evaluate the usefulness of WES in identifying the genetic etiology of congenital defects.

METHOD

WES was performed in 25 fetal samples with ultrasound anomalies and previous prenatal CGH-array with a normal result. Kit Nextera Flex for enrichment, oligos Illumina Exome using NextSeq (Illumina). Variant and segregation studies were confirmed by Sanger sequencing.

RESULTS

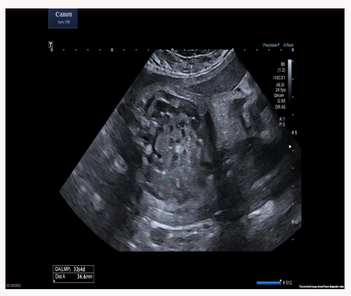
1. Global results:



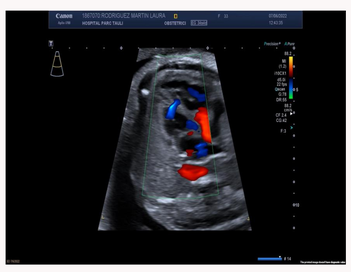
2. Pathogenic results:

Fetal phenotype	Variant	Gene	Pathogenicity	Inheritance	
Hidrocephaly, retrognatia, lordosis	c.2287_2321del	*EFTUD2*	Pathogenic	*de novo*	dominant
Focomelia	c.663+1G>A	*TBX5*	Pathogenic	paternal	dominant
Severe ventriculomegaly	c.2509C>T	*OFD1*	Pathogenic	paternal	dominant
Hydrops	c.716A>G hom	*SEC23B*	Pathogenic	carrier parents	recessive
IUGR, VSD, ectopic kidneys	c.2303T>C c.3788_3790del	*FANCA*	Pathogenic	carrier parents	recessive
NT>p99, hydrops	c.226G>C	*PTPN11*	Likely Pathogenic	*de novo*	dominant

IUGR: Intrauterine growth retardation, VSD: ventricular septal defect, NT: Nuchal translucency

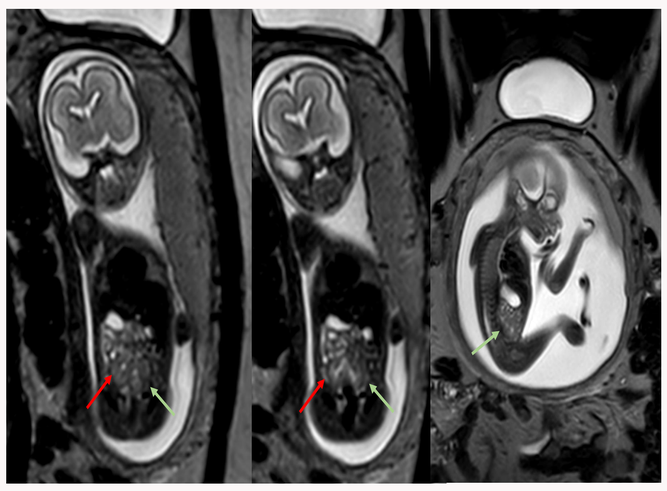


Ultrasound: : Pelvic fused ectopic kidney



Ultrasound: muscular VSD

Fetus with Fanconi anemia (c.2303T>*C FANCA*)



Magnetic resonance: Pelvic fused ectopic kidney (red arrow right kidney, green arrow left kidney

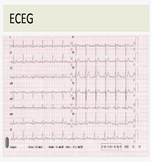
Fetus with Holt Oram syndrome (c.663+1G>A *TBX5*)

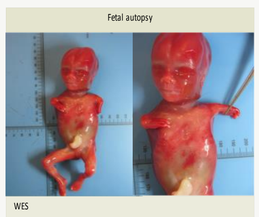
Focomelia, oligodactyly and congenital heart defect (ASD type OS and VSD).

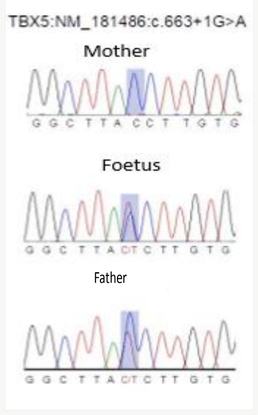
Holt Oram syndrome

- Limb defects (100%)
- Congenital defects (75%)
- Cardiac conduction abnormalities (sporadic)
- Complete penetrance
- Intrafamilial variability

Father
Bilateral hypoplasia of thumbs
Normal EEG







ASD: atrial septal defect, OS: ostium secundum

3. VUS results:

Fetal phenotype	Variant	Gene	Inheritance	
Aortic stenosis vs aorta coartation	c.13817A>G	*KMT2D*	maternal	dominant
Multicystic kidney	c.214A>T	*GLI3*	paternal	dominant
Lobar holoprosencephaly	c.5050T>C	*CNOT1*	No maternal	dominant

CONCLUSION

1. Despite the small sample size, the results show the clinical utility of prenatal WESfor detecting pathogenic/likely pathogenic variants in fetuses with congenital defects.
2. As in postnatal WES, detailed phenotyping is necessary to filter and prioritize variants to obtain a molecular diagnosis.

REFERENCES

1. **References:**Lord J et al. Prenatal exome sequencing analysis in fetal structural anomalies detected by ultrasonography (PAGE): a cohort study. Lancet 2019;393(10173):747-757. doi: 10.1016/S0140-6736(18)31940-8
2. Petrovski S et al. Whole-exome sequencing in the evaluation of fetal structural anomalies: a prospective cohort study Lancet 2019;393(10173):758-767. doi: 10.1016/S0140-6736(18)32042-7.
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