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Fetal exome sequencing in prenatal diagnosis

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Objective

To evaluate the usefulness of prenatal exome in pregnant women with fetal structural anomalies detected by ultrasound and normal chromosomal microarray analysis (CMA) in our center.

Methods

This was a retrospective observational study conducted in our Fetal Medicine Department at Parc Taulí University Hospital between January 2018 and August 2022. Pregnant women with diagnosis of fetal abnormality and a negative CMA or karyotype result were included. Blood samples from biological parents were also sent to the laboratory to be used for subsequent studies, if required. Genetic counselling was performed before (about the proposed genetic test and its advantages and limitations as incidental findings) and after the test.

Results

Fetal exome sequencing was performed in twenty-six pregnant women. The most common indications were: Twelve cases of multisystem anomalies (46%), four cases of complex heart diseases (15%) and three cases of complex anomalies of the central nervous system (12%). Gene panels were applied in seventeen cases (65%) and clinical exome sequencing in eight cases (35%). Exome sequencing provided an additional genetic result in eleven of them (42%). There were found two known pathogenic variants (18%), five likely pathogenic variants (46%) and four variants of uncertain significance (36%). Fetus with Noonan syndrome, Orofaciodigital syndrome type 1, Fanconi anemia, multiple pterygium syndrome and Holt-Oram syndrome were found as well as other probably pathogenic variants, but not related with specific syndromes. Regarding pregnancy outcomes, ten of the twenty-six pregnant women (38%) decided termination of pregnancy. Eight women (31%) decided to continue her pregnancy, delivering a living neonate. There were three cases of antepartum fetal death (12%).

Conclusion

Despite de small sample size, our results show the clinical utility of fetal exome sequencing in prenatal diagnosis, compared to the rest of the techniques used nowadays. It is an important tool in making decisions about the future of pregnancy, as well as neonatal management.

	NUMBER OF MALFORMATIONS	ORGAN OR SYSTEM AFFECTED	SONOGRAPHIC FINDINGS	PANEL VS EXOME	GENE	VARIANT TYPE	ASSOCIATED CONDITIONS	PERINATAL RESULTS	POSTNATAL ANALYSIS
1	Single	Heart	Aorta stenosis	Panel	KMTD2	VUS	Asplenia, intestinal malrotation, hearing loss	Living neonate	Bicuspid aorta valve, hypoplasia transverse aorta
2	Single	CNS	Hydrocephalus, cerebellum hypoplasia, Blake cyst	Exome	OFD1	Prob. Pat.	Orofaciodigital syndrome type 1	TOP (30 weeks)	-
3	Single	Heart	Hypoplasic right heart syndrome, pulmonary artery hypoplasia, ventricular septal defect,	Exome	CHRNA1	Prob. Pat.	Lethal multiple pterygium	Living neonate	Lost to follow-up
4	Single	Face	Harelip, cleft palate	Exome	GNB1	Prob. Pat.	Psychomotor delay; visual, gastrointestinal, genitourinary and cardiac malformations	Living neonate	Harelip, cleft palate, persistent ductus arteriosus
5	Single	Renal	Multicystic kidney	Exome	GLI3	VUS	Polydactyly, astrocytoma	Living neonate	Suspicion of Jarcho-Lewin syndrome
6	Polimarformations	CNS, face, limbs	Hydrocephalus, cerebellum hypoplasia, retrognathia, clubfoot	Exome	EFTUD2	Prob. Pat.	Mandibulofacial dysostosis-microcephaly syndrome	TOP (13 weeks)	-
7	Polimarformations	CNS, spine, face	Holoprosencephaly, hemivertebra, proboscis.	Exome	GLI2	VUS	Culler-Jones Syndrome, Holoprosencephaly	TOP (13 weeks)	-
8	Polimarformations	Spine, renal, abdominal wall	Hemivertebra, pelvic kidneys, omphalocele	Exome	ZNF423	VUS	Joubert syndrome, nephronophthisis	TOP (12 weeks)	-
9	Polimarformations	Heart, limbs	Phocomelia, congenital cardiac malformations	Exome	TBX5	Pat.	Holt-Oram syndrome	TOP (17 weeks)	-
10	Polimarformations	Heart, limbs	Heart chambers asymmetry,	Panel	PTPN11	Pat.	Noonan syndrome	TOP (12 weeks)	-
11	Polimarformations	Heart, renal, IUGR	Horseshoe kidney, IUGR, ventricular septal defect	Exome	FANCA	Prob. Pat.	Fanconi anemia	TOP (39 weeks)	-