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# The Importance of Clinical Exome Sequencing for Prenatal Diagnosis: A case report

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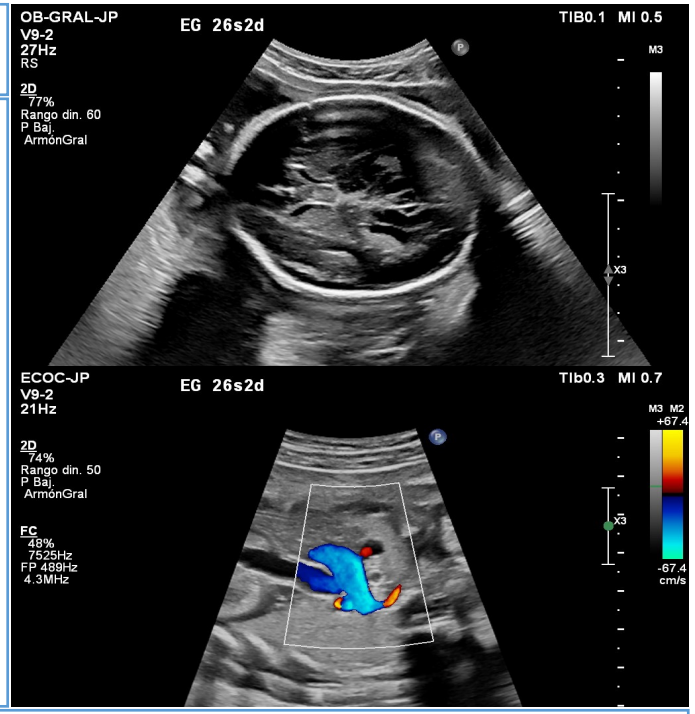
**OBJECTIVE:** To report a case that highlights the importance of clinical exome sequencing in cases where nuchal translucency (NT) is greater than the 99th percentile and where other ultrasound findings are present throughout gestation, despite normal results from QF-PCR and chromosomal microarray analysis.

**CASE REPORT:** A 31-year-old pregnant woman was referred to our hospital at 21+3 weeks for evaluation due to a diagnosis of aberrant right subclavian artery (ARSA) on early echocardiography (16 weeks) for NT>p99 in the first-trimester ultrasound, as well as evidence of ecogenic cavum of the septum pellucidum and agenesis of ductus venosus in the morphological ultrasound. In the first-trimester ultrasound, a NT of 3.9 mm (>p99) was detected. For this reason, a chorionic biopsy was performed to analysis QF-PCR and chromosomal microarray, all of which were normal. Neurosonography confirmed ecogenic cavum of the septum pellucidum with no other central nervous system abnormalities. Echocardiography revealed the presence of ARSA and a ductus venosus agenesis.

The case was presented to our Fetal Medicine Committee and it was decided that the patient met the criteria for clinical exome sequencing. Two variants were detected; a missense variant near the RAF1 splicing site that was classified as a variant of uncertain significance (VUS) and another missense in FGFR2, which was classified as probably pathogenic since a pathogenic variant in the same amino acid had been identified in a patient with syndromic craniosynostosis.
In the segregation study of the progenitors, the RAF variant was found to be de novo and was therefore classified as probably pathogenic. Mutations in RAF1 are associated with Noonan syndrome and, in some cases, with LEOPARD syndrome. In contrast, the FGFR2 variant was inherited from the father. For this reason, a medical history of the progenitor was conducted, ruling out dysmorphic and neurodevelopmental disorders. Considering this information, it was classified as a VUS.

MRI at 29 weeks showed extensive bilateral cortical developmental abnormality, including bilateral fronto-parietal and temporal cortex, as well as asymmetric rotation of the hippocampi. No alterations were observed in the corpus callosum or in the cavum of the septum pelludicum. A report was made to request the legal termination of the late pregnancy, which was approved and carried out at 31 weeks' gestation. The fetal autopsy confirmed the presence of an ARSA and agenesis of the ductus venosus with interhepatic drainage. In addition, low implantation of the ears was observed with no evidence of hypertelorism. However, no signs of delayed cortical maturation were observed either macroscopically or histologically.




**DISCUSSION:** Currently, karyotype and microarrays are routinely performed when fetal malformations are observed. The detection rate depends on the abnormality identified by ultrasound. For example, if the NT measurement is greater than 3.5mm, 30-50% of cases have an abnormal QF–PCR result. However, if it is normal, subsequent pathogenic microarray shows an incremental yield of only 2-4% in cases of an apparently isolated increased NT. Therefore, genetic alterations are not detected in many cases, leaving families without a clear diagnosis and only counselling based on ultrasonography findings.
Prenatal whole exome sequencing (WES) has the potential to provide a more precise diagnosis, improving the ability to counsel families. However, this testing presents significant challenges, such as the interpretation of variants, incidental findings in the parents and/or fetus, or the impact on family members and responsibility for future re-analysis. The indications for sequencing the exome in prenatal setting are still being discussed. The International Society of Prenatal Diagnosis, the Society of Maternal Fetal Medicine and the Perinatal Quality Foundation state that the use of diagnostic sequencing is currently being introduced for evaluation of fetuses for whom standard diagnostic genetic testing, such as chromosomal microarray analysis, has already been performed and is uninformative. Prior to undergoing exome sequencing, it is crucial to sign an informed consent form and explain the potential results that may be obtained. It is strongly advised that a multidisciplinary team interpret the findings, and all families receive counseling from a provider with genetics expertise.

**CONCLUSION:** The routine use of karyotype and microarrays when fetal malformations are observed may not detect many of the genetic alterations, leaving families without a clear diagnosis. WES has the potential to provide a more precise diagnosis. However, it presents significant challenges, and its indications are still under debate. In summary, it is indicated for fetuses with multiple ultrasound malformations and the standard genetic testing are normal. Interpretation of WES results should be carried out by a multidisciplinary team, and families should receive counselling from a provider with genetics expertise.