

POSTER EP 10.75

PRENATAL DIAGNOSIS OF MIRAGE SYNDROME: GENOTYPE AND PHENOTYPE DISPARITY OF SAMD9 MUTATION AND NEONATAL OUTCOME

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INTRODUCTION

MIRAGE syndrome — an acronym for Myelodysplasia, Infections, Restriction of growth, Adrenal hypoplasia, Genital phenotypes, and Enteropathy — is a rare and potentially lethal autosomal-dominant disorder caused by de novo heterozygous gain-of-function mutations in SAMD9, located on chromosome 7q21.2. We report a prenatal case with phenotype-genotype disparity

Tanase-Nakao, K., Olson, T. S. & Narumi, S. (2020). MIRAGE Syndrome - GeneReviews® - NCBI Bookshelf. GeneReviews®. <https://www.ncbi.nlm.nih.gov/books/NBK564655/>

CASE PRESENTATION

A 39-year-old gravida 4, para 3 woman with three previous Cesarean deliveries presented at 29 weeks of gestation with fetal short long bones. Her first child had hydrocephalus and cerebral palsy.

First trimester (13 weeks) and mid-trimester (19 weeks) anomaly scans were unremarkable. Non-invasive prenatal testing (NIPT) was offered but declined by the couple. At 29 weeks, fetal growth assessment demonstrated a shortened femur-to-foot length, normal abdominal circumference, and an abnormal femur-to-head circumference ratio, findings suggestive of mild skeletal dysplasia. No additional structural abnormalities were identified.

PRENATAL DIAGNOSIS

Amniocentesis was performed, and the sample was sent for Whole Exome Sequencing (WES). The results identified a pathogenic variant in the SAMD9 gene, which is associated with MIRAGE syndrome and a potentially poor prognosis. The patient was informed of these findings and referred to a geneticist for counseling. The geneticist recommended a conservative approach, considering fetal growth restriction as a more likely diagnosis than MIRAGE syndrome, and advised postnatal assessment.

NEONATAL OUTCOME

The patient underwent an elective Cesarean section at 37 weeks of gestation due to stage 1 (Barcelona) fetal growth restriction and delivered a healthy female infant weighing 2.5 kg with normal external genitalia. Postnatal evaluation revealed short limbs and a small patent foramen ovale (PFO). The infant remained clinically stable until day 4 of life, after which she was discharged and followed up as an outpatient.

GENETIC ANALYSIS

Whole exome sequencing identified a likely pathogenic variant in one allele of the SAMD9 gene (NM_017654.4:c.998G>A; p.Trp333*) in the fetus. This variant introduces a premature stop codon, resulting in a truncated protein. Although loss-of-function (LoF) variants in SAMD9 are generally classified as likely pathogenic according to ACMG guidelines, MIRAGE syndrome is primarily associated with gain-of-function (GoF) mutations. Therefore, this variant is unlikely to cause MIRAGE syndrome despite in silico predictions of pathogenicity. To address the observed phenotype-genotype discrepancy, genetic counseling was provided and whole exome sequencing (WES) Trio analysis was pursued. Parental testing revealed that the healthy mother is homozygous for the variant, confirming its benign nature in this context.

CONCLUSION:

This case highlights a critical phenotype-genotype disparity in SAMD9 interpretation, underscoring the need for multidisciplinary input and careful correlation between sonographic findings and molecular results.