JAMA Ophthalmology Clinical Challenge

# Incidental Genetic Finding in a Fetus

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**A 37-year-old woman,** gravida 1 para 0, at 29 weeks' gestation, underwent amniocentesis due to a suspected polycystic kidney detected on routine fetal ultrasonography. While no genetic abnormality associated with polycystic kidney was identified (whole-exome sequencing Invitae), an incidental finding of a heterozygous c.501-2 A<G sequence variant (SV) in the *RB1* gene was noted. This specific *RB1* SV had not been previously reported in any genetic databases, but was deemed pathogenic by Invitae, the commercial laboratory, in line with the American College of Medical Genetics and their guidelines for interpretation of sequence variants.[1] No intraocular tumors were found on fetal sonography. There was no discernable family history of retinoblastoma or ocular disorders, and complete ophthalmic evaluation of both parents was normal with no suspected retinomas.

**WHAT WOULD YOU DO NEXT?**

- **A.** Plan for early delivery
- **B.** Continue routine prenatal follow-up
- **C.** Further genetic evaluation of the fetus and parents
- **D.** Advise pregnancy termination

CME Quiz at jamacmelookup.com

## Diagnosis

***RB1* pathogenic sequence variant in a 29-week-old fetus with no family history or sonographic features suggestive of retinoblastoma.**

## What to Do Next

**C.** Further genetic evaluation of the fetus and parents

## Discussion

Retinoblastoma, with an incidence of 1 in 17 000 live births, is typically diagnosed within a few years of life.[2] Early treatment can lead to nearly 100% survival rate. Prognosis is poor with delayed diagnosis or treatment.[2] Inherited retinoblastoma occurs at a younger age than sporadic disease, tends to be bilateral,[3] and results from biallelic pathogenic SVs (PSVs) in the *RB1* gene in a precursor retinal cell.[4,5] An inherited mutated allele (ie, germline PSV) predisposes to tumorigenesis in utero or after birth in 40% of retinoblastoma cases, with high penetrance of the disease.[3,5,6]

Current evidence suggests screening at-risk newborns (ie, those with a family history of retinoblastoma) until 4 years of age.[7] Prenatal molecular screening facilitates earlier detection, potentially improving family planning, genetic counseling, and earlier interventions.[4,8] For example, planned delivery for prenatally confirmed carriers of *RB1* mutations can lead to earlier diagnosis, reduced treatment-associated morbidity, and favorable visual outcomes.[4] However, early fetal delivery has potential risks, including physical and neurocognitive delay, warranting cautious evaluation by multidisciplinary teams.[4,8] Furthermore, while no threshold exists for planned early delivery, premature delivery may be achieved effectively with active intervention following 26 weeks' gestation.[9]

Inactivating *RB1* germline PSVs have been associated with high penetrance, with most PSV carriers developing intraocular tumors by early childhood. However, phenotypic presentation may differ among individuals, even among identical PSV carriers.[3,6] Alekseeva et al[6] reported a substantial prevalence of asymptomatic mutated *RB1* PSV carriers among parents of retinoblastoma patients with more children inheriting a defective *RB1* gene from the father, suggesting parental origin may affect retinoblastoma penetrance. In another study, individuals harboring low-penetrance *RB1* PSVs (eg, splice-site and missense SVs) developed bilateral retinoblastoma later than patients with null PSVs.[4] Molecular screening methods (eg, RNA sequencing of amniotic fluid cells) have enabled clinicians to assess whether a specific *RB1* SV is likely to be associated with any phenotypic manifestations.[10] However, there currently are no clinically acceptable predictive parameters to better define the phenotypic expression of *RB1* PSV carriers. The case presented herein reports an incidental *RB1* PSV detected on unrelated genetic testing, posing a clinical and ethical dilemma to both clinician and family.[3,4,6,8]

## Outcome

Both parents underwent whole-exome sequencing (choice C), confirming the father, with no history of cancer, harbored the same genetic SV as the fetus, decreasing the possibility that the SV was pathogenic. RNA sequencing demonstrated disruption of the splice site, resulting in shortened protein product; however, the reading frame remained intact. Based on these 2 features, the SV was downgraded as a variant of undetermined significance. Due to inconclusive evidence that the specific SV was pathogenic, pregnancy termination was not recommended (choice D). Pregnancy termination is a multifaceted subject with psychosocial, cultural, and medical implications, differing across communities worldwide and beyond the scope of this discussion. Following a multidisciplinary evaluation, the fetus was not delivered prematurely, noting associated risks of early fetal delivery, lack of radiological evidence of intraocular tumors, and further genetic evaluation downgrading pathogenicity of the incidental variant (choice A). Routine prenatal observation without ad-

ditional investigations for suspicious intraocular pathologies may not be sufficient to rule out retinoblastoma and was therefore performed in collaboration with clinical geneticists and multimodal fetal imaging (choice B). Follow-up fetal magnetic resonance imaging performed at 38 weeks' gestation did not demonstrate any intraocular tumors or intracranial abnormalities suggesting trilateral retinoblastoma.

The parents decided to continue the pregnancy. The child was born at 39 weeks and 6 days without complications. Examination demonstrated no evidence of intraocular tumors but was not performed under anesthesia per the parents' request. The child, currently aged 10 months, continues to be evaluated periodically to rule out retinoblastoma, and is currently without any pathogenic ocular abnormalities.

## ARTICLE INFORMATION

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