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J Case Rep Images Opthalmol 2026 Jul-Dec;9(2):11–16.
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Ophthalmic manifestations of MAB21L2 mutation: A case report

AbdalWahab AlEnezy, Aseel AlKandari, Alaa AlAli

ABSTRACT

Introduction: This report is to describe the clinical presentation, ophthalmic findings, and multimodal evaluation of a child with severe bilateral microphthalmia and coloboma associated with a MAB21L2 variant.

Case Report: A 3-year-old girl presented with bilateral small eyes and abnormal eye movements. Examination showed chin-up posture, bilateral ptosis, large-angle non-accommodative esotropia, limitation of abduction, wandering nystagmus, xanthocoria on Bruckner test, microcornea [8 mm OD (right eye), 6.5 mm OS (left eye)), sclerocornea superiorly with clear central cornea, bilateral inferonasal iris coloboma, and inferior lens subluxation with zonular disruption. Fundus examination revealed a severely disorganized retina with retinal cysts and folds and inferior chorioretinal coloboma. Intraocular pressure (IOP) was 21 mmHg OD and 19 mmHg OS. A B-scan revealed taut retinal folds with a retinal cyst in the OD and a retinal cyst in the OS. Magnetic resonance imaging (MRI) orbit/brain showed small globes [measuring about 11–12 mm in anteroposterior diameter (AP)], with multiple retrobulbar cysts encroaching on the optic nerve sheath complex, bilateral optic nerve hypoplasia (<1 mm intraorbital, 1.5 mm cisternal), and a small optic chiasm, with no brain malformations. Genetic testing via Sanger sequencing revealed an apparently homozygous variant in MAB21L2, c.749G>T p.(Cys250Phe).

Conclusion: This case illustrates a severe microphthalmia and coloboma spectrum disorder with extensive anterior and posterior segment dysgenesis and marked optic nerve hypoplasia. Serial examination under anesthesia (EUA) and multimodal imaging were of the essence for complete characterization and follow-up. The familial pattern and MAB21L2 finding provide a unifying developmental explanation for the case.

Keywords: Coloboma, MAB21L2 mutation, Microphthalmia, Ophthalmic manifestations, Optic nerve hypoplasia

How to cite this article

AlEnezy A, AlKandari A, AlAli A. Ophthalmic manifestations of MAB21L2 mutation: A case report. J Case Rep Images Opthalmol 2026;9(2):11–16.

Article ID: 100056Z17AA2026

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doi: 10.5348/100056Z17AA2026CR

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Received: 28 May 2026
Accepted: 06 July 2026
Published: 07 August 2026

INTRODUCTION

Microphthalmia and coloboma represent a spectrum of congenital ocular developmental anomalies arising early in the development of the optic vesicle due to a failure of the optic fissure to close [1, 2]. Widespread clinical severity ranges from mild iris defects to profound maldevelopment affecting the lens, retina, optic nerve, and orbit [2, 3]. Both careful clinical evaluation and high-resolution orbital MRI have become essential for defining these structural abnormalities, providing an estimation of visual prognosis, and differentiating isolated ocular disease from syndromic malformations [3, 4].

Here, we present a 3-year-old child with an extremely complex ocular phenotype consisting of bilateral

microphthalmia, coloboma, lens subluxation, and optic nerve hypoplasia. A similarly affected sibling and the presence of an apparently homozygous MAB21L2 variant point toward a familial developmental disorder [4].

CASE REPORT

A 3-year-old female was referred to our center for evaluation of bilateral small eyes with abnormal eye movement. Upon history, the mother noted that the patient was born with small eyes and was referred to a pediatric ophthalmologist for non-accommodative esotropia. The mother mentioned that the patient is the fourth child of a consanguineous marriage, and her older brother has unilateral microphthalmia. On examination, she had a chin-up position, a flat nasal bridge, bilateral ptosis, large angle esotropia of more than 20 prism diopters with bilateral limitation in abduction, along with wandering nystagmus. Xanthocoria was noted on the Bruckner test. Slit lamp examination showed normal adnexal tissue in both eyes, sclerocornea with a clear central cornea, and a horizontal corneal diameter of 8 mm in the right eye and 6.5 mm in the left eye. Anterior segment dysgenesis was noted bilaterally with inferonasal iris coloboma and bilateral subluxated crystalline lenses inferiorly with broken zonules (Figure 1). Dilated fundus exam showed a disorganized anomalous retina with bilateral retinal cysts and folds and a chorioretinal coloboma inferiorly. Intraocular pressure was 21 mmHg in the right eye and 19 mmHg in the left eye, respectively. A B-scan of the right eye showed a retinal detachment and taut retinal folds with retinal cysts, while the left eye showed retinal cysts (Figures 2 and 3). An MRI of the orbit and brain showed a small globe with an 11–12 mm maximum AP diameter. Multiple cysts were noted bilaterally encroaching on the optic nerve sheath complex. Both optic nerves are slender in shape and measured less than 1 mm in thickness at the orbital segment and 1.5 mm at the cisternal segment with a small optic chiasm (Figures 4 and 5). No other definite brain malformations are noted.

A complete skeletal survey demonstrated normal vertebral alignment, normal long-bone morphology, intact cranial sutures, and age-appropriate bone development, with no evidence of skeletal dysplasia. Genetic testing with Sanger sequencing was done to detect chr4:151504930, c.749G>T p.(Cys250Phe) in Ex1 of MAB21L2 (NM_006439.4) gene, and it showed apparent homozygous for c.749G>T in the MAB21L2 gene. The patient was scheduled for serial examinations every six months, including intraocular pressure assessments, fundus evaluations, and ocular motility assessments. The family was advised to receive genetic counseling. Over a follow-up period of 12 months, the retinal cysts remained stable, and no new ocular or systemic complications developed.

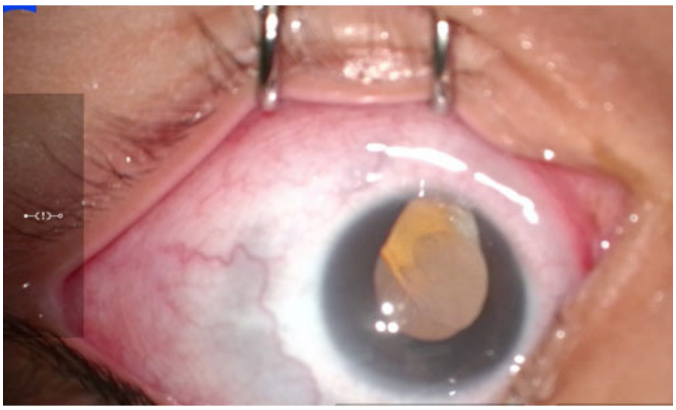

Figure 1: Dilated EUA of the right eye showing lens subluxation and zonular dehiscence.

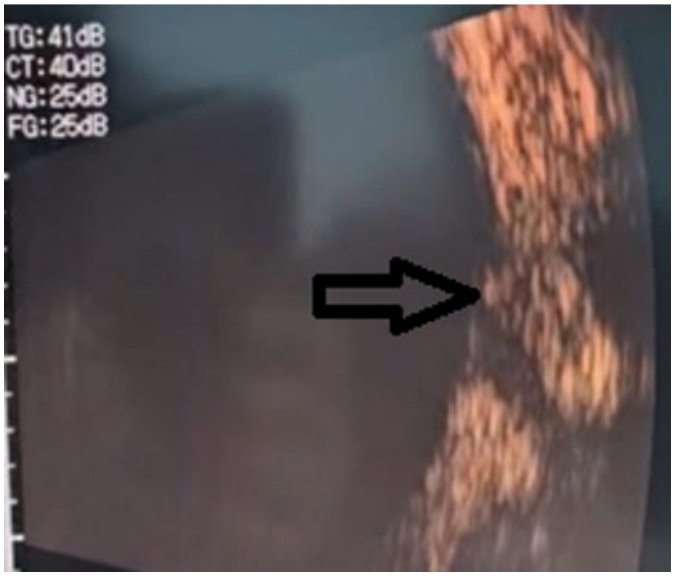

Figure 2: B-scan of left eye shows a calcified retinal cyst (black arrow).

Figure 3: B-scan of the right eye demonstrating retinal detachment (black arrow).

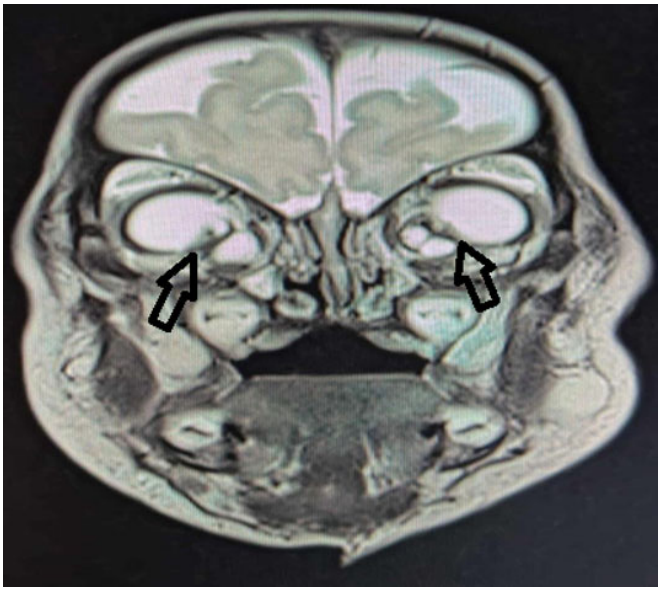

Figure 4: Coronal T2 MRI showing bilateral microphthalmia (black arrows), with small globes measuring approximately 11–12 mm in AP diameter.

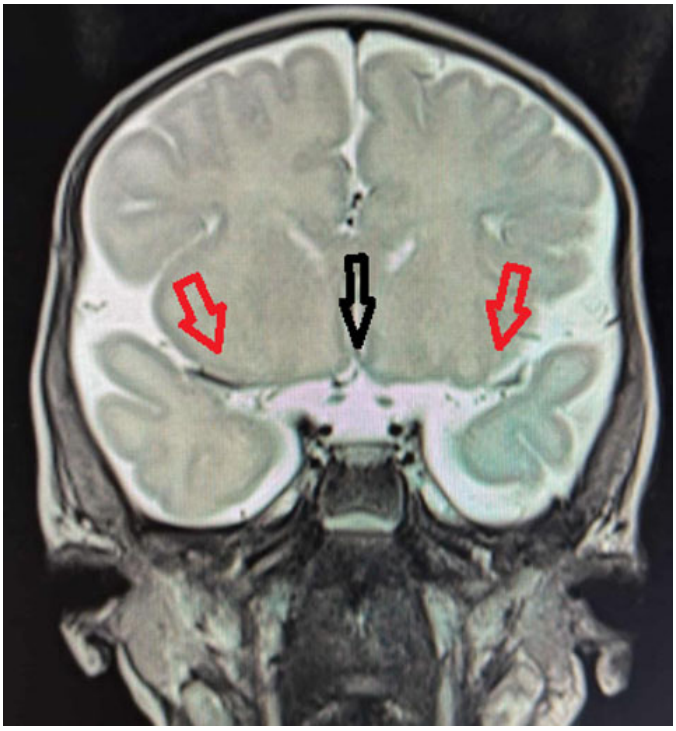

Figure 5. Coronal T2 MRI showing bilateral optic nerve hypoplasia (red arrows). The optic nerves appear markedly slender with small optic chiasm (black arrow).

DISCUSSION

Microphthalmia and coloboma represent congenital ocular anomalies with varied severity. In many children, the abnormalities are confined to a single structure, such as the iris or retina, and the visual outcome may be reasonably preserved [5]. In contrast, more severe forms involve multiple ocular structures and reflect early and widespread disruption of eye development [1, 6]. Microphthalmia, anophthalmia, and coloboma (MAC) are a spectrum of severe congenital eye defects caused by highly heterogeneous genetic networks that regulate early eye development [7]. The 11–12 mm AP globe diameter in this patient was markedly below the mean ocular axial length of 21.8 mm reported at three years [8]. The patient showed the most extreme global presentation that has been seen in this spectrum. The occurrence of prominent microphthalmia, microcornea, superior sclerocornea, inferonasal iris coloboma, inferior lens subluxation, and large retrobulbar colobomatous cysts points to a primary failure of signaling during early stages of optic vesicle patterning and embryonic fissure closure. Such extensive involvement is uncommon and is usually associated with limited visual potential [7].

The posterior segment findings were particularly notable. The presence of retinal folds, retinal cysts, and inferior chorioretinal coloboma is characteristic of advanced fissure-closure defects. In severe cases, dysplastic ocular tissue may herniate through the coloboma, forming colobomatous cysts [9, 10]. In our patient, retrobulbar cysts were clearly identified on MRI, emphasizing the value of imaging in fully characterizing the extent of disease. These cysts may change in size over time and are often underrecognized without imaging [11]. Another key feature was the profound bilateral optic nerve hypoplasia. Pediatric MRI data report a mean optic nerve diameter of 2.9 ± 0.4 mm at 3 to <4 years when measured 3 mm posterior to the globe [12]; the patient's intraorbital measurement of <1 mm is therefore markedly reduced, although the 1.5 mm cisternal measurement is not directly comparable because it was obtained at a different site. Both optic nerves were markedly thin, with an associated small optic chiasm. Optic nerve hypoplasia is a known association of microphthalmia and posterior coloboma and is thought to result from reduced retinal ganglion cell development or early disruption of the optic stalk [13]. Magnetic resonance imaging plays an important role in confirming optic nerve hypoplasia and provides useful prognostic information [14]. In this case, the degree of optic nerve underdevelopment strongly suggests poor visual potential. The anterior segment abnormalities, including microcornea and inferior lens subluxation with zonular weakness, further support the presence of widespread developmental involvement. Lens subluxation in this context likely reflects abnormal zonular development as part of anterior segment dysgenesis rather than an isolated lens disorder [15].

Because of the child's young age, poor fixation, nystagmus, and complex ocular anatomy, EUA was necessary. EUA allowed accurate assessment of corneal dimensions, lens position, intraocular pressure, and posterior segment anatomy, which could not be reliably evaluated in the clinic. Serial examination under anesthesia (EUA) examinations were also important for monitoring the stability of the lens, as well as the

retinal cysts and folds, and for surveillance of potential complications such as glaucoma. Brain MRI and skeletal survey were normal despite extensive ocular findings. This information is clinically relevant, since most of the syndromic conditions associated with microphthalmia and coloboma have associated central nervous system or skeletal abnormalities [16]. Additionally, there is no systemic involvement that supports the diagnosis of non-syndromic ocular maldevelopment.

For better understanding of this case, the molecular pathology of MAB21L2 will be explored. The MAB21L2 gene of human origin, located on chromosome 4q31.3, encodes a highly conserved 41 kDa nuclear protein that acts as a transcriptional co-repressor and cell-fate determining factor during optic cup morphogenesis. MAB21L2, which is a globuler protein internally has an N-terminal nucleotidyltransferase-like domain that mediates important protein–protein interaction and nucleic acid binding [17]. Current research has explored whether the MAB21L2 variants act via a dominant-negative or recessive loss-of-function mechanism can influence the phenotypic severity and systemic involvement, with important clinical implications.

A mutation in this single-exon gene is an exceedingly rare cause of ocular maldevelopment in man, with fewer than 30 distinct clinical cases reported in the world literature in isolated families [4, 17, 18]. Most of the reported human MAB21L2 cases involve de novo heterozygous missense mutations that cluster at a highly sensitive N-terminal hotspot, specifically at Arg51 and Glu49 residues [4, 18]. These mutations affect important intramolecular salt bridges, destabilizing the protein but leaving enough structure intact to bind and poison wild type complexes of the protein [19]. As a result, these heterozygous variants feature severe Syndromic Microphthalmia 14 which presents with total anophthalmia or microphthalmia with prominent extraocular malformations rhizomelic skeletal dysplasia, intellectual disability and cleft palate [4, 19]. By contrast, mutations in sites outside of this N-terminal hotspot generally yield a less toxic, hypomorphic loss-of-function profile requiring a homozygous state to manifest [4, 18]. The variant c.749G>T p.(Cys250Phe) of our patient is located at the central-to-C′-terminal part of the protein and the substitution of the highly conserved cysteine 250 with a bulky phenylalanine is expected to disturb folding at this local site, resulting in a severe loss of functional protein.

Our case has several similarities but also important differences that clarify the developmental mechanism when compared to classical cases where heterozygous mutations resulted in a severe multi-systemic skeletal and intellectual phenotype [4, 19]. Unlike the previous cases, the homozygous phenotype of our patient is limited only to the eye. It is similar to that of a homozygous p.Arg247Gln case, which was also only limited to the eye and spared systemic tissue as well [18]. The tissue-specific threshold for MAB21L2 expression during skeletal development is extremely permissive. In sharp contrast, the embryonic eye requires absolute molecular perfection. Any slight hypomorphic loss-of-function can result in global ocular collapse.

The cysts that are multi-locular that occur in the retrobulbar region and encroach upon the optic nerve sheath complex represent a localized pathomechanism that is severe and unique to this expanded phenotype. Heavy expression of MAB21L2 occurs in the neural retina and ventral optic stalk during early embryogenesis. Knockout zebrafish models indicate that the loss of this gene prevents basement membrane degradation at the sides of the embryonic choroid fissure [20]. As a result, the split does not fuse properly, allowing primitive dysplastic neuro-retinal tissue to herniate through the defect. Because of intraocular fluid pressure, the tissue herniated and expanded into the retrobulbar space, which formed the large and tense cysts seen on imaging.

Moreover, the anterior segment anomalies in this patient with an inferior lens subluxation and zonular dehiscence are unusually severe compared to the cataracts reported in cases of dominant inheritance [19]. MAB21L2 regulates the upstream networks of Pax6 and Pitx3 in the lens placode [18]. Hypomorphic expression of these factors inhibits the early ciliary body differentiation and zonular fiber synthesis, leading to structural ectopia lentis. The involvement of bilateral optic nerve hypoplasia results in an arrest in neurogenesis. Animal studies indicate that MAB21L2 has distinct stage-dependent functions, first maintaining retinal progenitor cell proliferation and then timing the initiation of retinogenesis through controlling the bHLH factors ATOH7 and NEUROD4. At this point of development, disruption leads to abnormal specification of retinal ganglion cells and severe hypoplasia of pre-chiasmatic optic nerves [17, 18].

In summary, this case illustrates a stepwise approach to ophthalmic management, putting together careful clinical examination, serial EUA, and multimodal imaging to fully delineate complex congenital ocular anomalies. Etiology can be explored with targeted genetic testing and family counseling. Through comparison with previous studies, we showed that the apparently homozygous p.Cys250Phe variant expands the known MAB21L2 disease spectrum. The study shows that autosomal recessive variants can cause severe pan-ocular collapse, with lens subluxation, retinal detachment, and retrobulbar cysts.

CONCLUSION

This case describes a child with a very severe form of congenital maldevelopment of the eyes, including microphthalmia, coloboma, anterior and posterior segment maldevelopment, and very severe hypoplasia of the optic nerves. While the condition was non-syndromic because brain and skeletal abnormalities were absent, the presence of a homozygous MAB21L2 mutation explains the developmental pathophysiology for this case. This

case underlines the need for a systematic approach and the utility of a combination of imaging studies and molecular analysis in children with very complicated congenital abnormalities of the eyes.

REFERENCES

1. Williamson KA, FitzPatrick DR. The genetic architecture of microphthalmia, anophthalmia and coloboma. Eur J Med Genet 2014;57(8):369–80.
2. Skalicky SE, White AJR, Grigg JR, Martin F, Smith J, Jones M, et al. Microphthalmia, anophthalmia, and coloboma and associated ocular and systemic features: Understanding the spectrum. JAMA Ophthalmol 2013;131(12):1517–24.
3. Harding P, Gore S, Malka S, Rajkumar J, Oluonye N, Moosajee M. Real-world clinical and molecular management of 50 prospective patients with microphthalmia, anophthalmia and/or ocular coloboma. Br J Ophthalmol 2023;107(12):1925–35.
4. Rainger J, Pehlivan D, Johansson S, Bengani H, Sanchez-Pulido L, Williamson KA, et al. Monoallelic and biallelic mutations in MAB21L2 cause a spectrum of major eye malformations. Am J Hum Genet 2014;94(6):915–23.
5. Nakamura KM, Diehl NN, Mohney BG. Incidence, ocular findings, and systemic associations of ocular coloboma: A population-based study. Arch Ophthalmol 2011;129(1):69–74.
6. Gregory-Evans CY, Williams MJ, Halford S, Gregory-Evans K. Ocular coloboma: A reassessment in the age of molecular neuroscience. J Med Genet 2004;41(12):881–91.
7. Bardakjian TM, Schneider A. The genetics of anophthalmia and microphthalmia. Curr Opin Ophthalmol 2011;22(5):309–13.
8. Groot ALW, Lissenberg-Witte BI, van Rijn LJ, Hartong DT. Meta-analysis of ocular axial length in newborns and infants up to 3 years of age. Surv Ophthalmol 2022;67(2):342–52.
9. Chaudhry IA, Arat YO, Shamsi FA, Boniuk M. Congenital microphthalmos with orbital cysts: Distinct diagnostic features and management. Ophthalmic Plast Reconstr Surg 2004;20(6):452–7.
10. Al-Khamiss A, Ayoubi A, Manzoor M, Al-Dandan S. Colobomatous cyst: Histopathological characterization. J Case Rep Images Pathol 2015;1:12–6.
11. Vegunta S, Patel BC. Optic nerve coloboma. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2026.
12. Janthanimi P, Dumrongpisutikul N. Pediatric optic nerve and optic nerve sheath diameter on magnetic resonance imaging. Pediatr Radiol 2019;49(8):1071–7.
13. Borchert M. Reappraisal of the optic nerve hypoplasia syndrome. J Neuroophthalmol 2012;32(1):58–67.
14. Salman MS, Hossain S, Rozovsky K. Neuroimaging features in children with optic nerve hypoplasia and septo-optic-pituitary dysplasia. Can J Neurol Sci 2024;51(3):416–24.
15. Reis LM, Semina EV. Genetics of anterior segment dysgenesis disorders. Curr Opin Ophthalmol 2011;22(5):314–24.
16. Slavotinek A. Genetics of anophthalmia and microphthalmia. Part 2: Syndromes associated with anophthalmia-microphthalmia. Hum Genet 2019;138(8–9):831–46.
17. Ceroni F, Cicekdal MB, Holt R, Sorokina E, Chassaing N, Clokie S, et al. Deletion upstream of MAB21L2 highlights the importance of evolutionarily conserved non-coding sequences for eye development. Nat Commun 2024;15(1):9245.
18. Sghari S, Gunhaga L. Temporal requirement of Mab21l2 during eye development in chick reveals stage-dependent functions for retinogenesis. Invest Ophthalmol Vis Sci 2018;59(10):3869–78.
19. Deml B, Kariminejad A, Borujerdi RHR, Muheisen S, Reis LM, Semina EV. Mutations in MAB21L2 result in ocular coloboma, microcornea and cataracts. PLoS Genet 2015;11(2):e1005002.
20. Gath N, Gross JM. Zebrafish mab21l2 mutants possess severe defects in optic cup morphogenesis, lens and cornea development. Dev Dyn 2019;248(7):514–29.

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Author Contributions

AbdalWahab AlEnezy – Conception of the work, Design of the work, Acquisition of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Aseel AlKandari – Design of the work, Acquisition of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Alaa AlAli – Design of the work, Acquisition of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

None.

Consent Statement

Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest
Authors declare no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.

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