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Online-Only Material: The video is available at <http://www.jamaophth.com>.

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Mutation of *GNAQ* in a Cytologically Unusual Choroidal Melanoma in an 18-Month-Old Child

Fewer than 1% of uveal melanomas (UMs) occur in patients younger than 20 years.¹ We report a histologically unusual UM in a child that was confirmed by the presence of a *GNAQ* somatic mutation.

Report of a Case. An 18-month-old girl was referred to an ophthalmic oncologist after being diagnosed as having leukokoria of the right eye. Her mother felt that the eye was "lazy" from birth. At 6 months, a nurse noticed an abnormal red reflex. The child was first seen by an ophthalmologist 12 months later when it was noticed that the affected pupil was dilated. Magnetic resonance imaging showed a uniformly enhancing right intraocular mass (**Figure 1A-C**). Examination under anesthesia revealed a total retinal detachment with a yellow subretinal mass. A preliminary diagnosis of retinoblastoma was

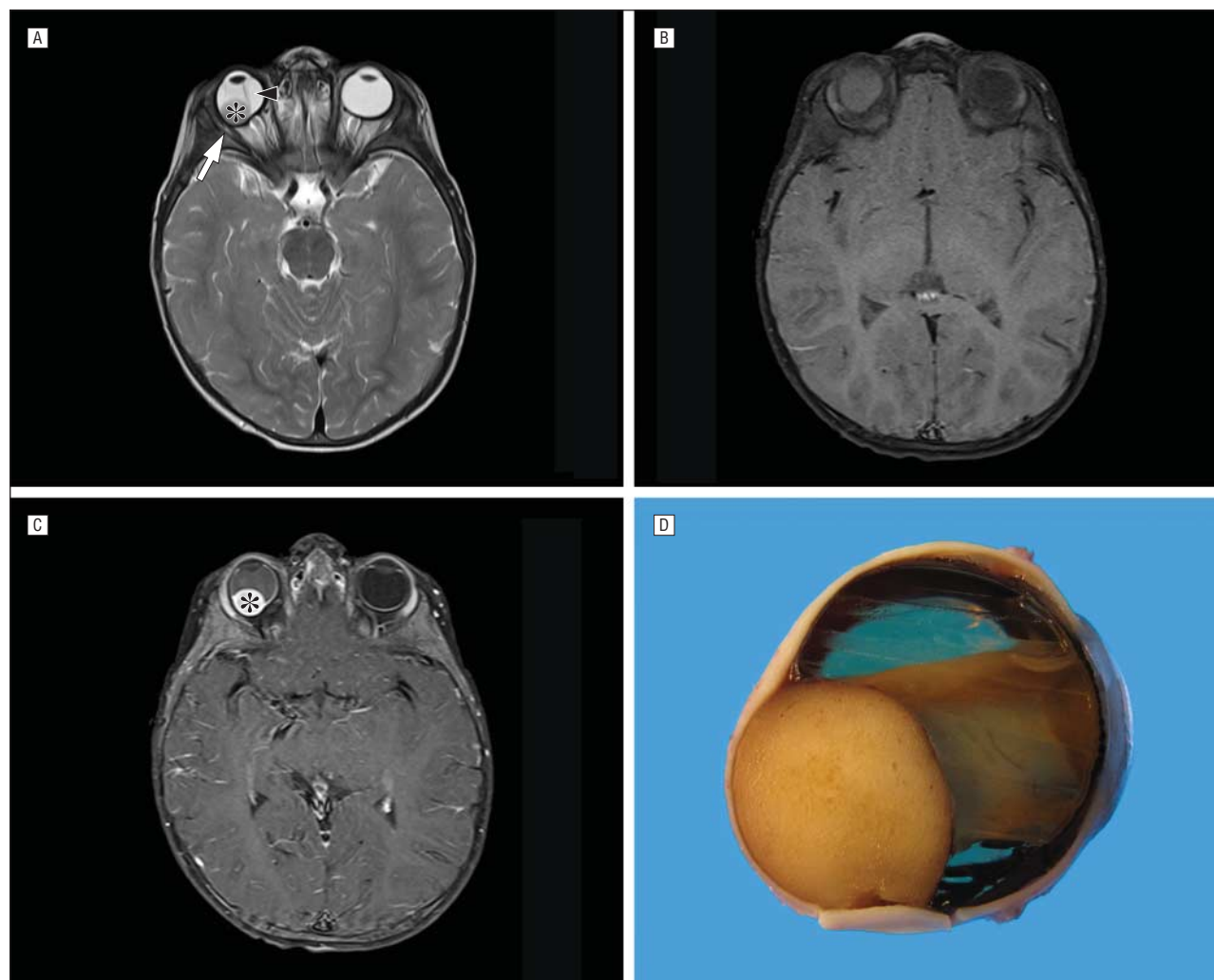


Figure 1. Magnetic resonance images and clinical photograph. Axial non-fat-saturation T2-weighted (A), contrast-enhanced T1-weighted (B), and axial fat-saturation T1-weighted (C) magnetic resonance images show a uniformly enhancing right intraocular mass (asterisks in A and C). Note the deformation of the sclera adjacent to the mass (arrow in A), with no evidence of scleral, extrascleral, or optic nerve extension. The right globe is smaller than the left. The retinal detachment is well seen (arrowhead) on the T2-weighted image (A). D, The enucleated globe shows a solid cream-colored tumor in the posterior choroid. Note the complete retinal detachment and gelatinous subretinal fluid.

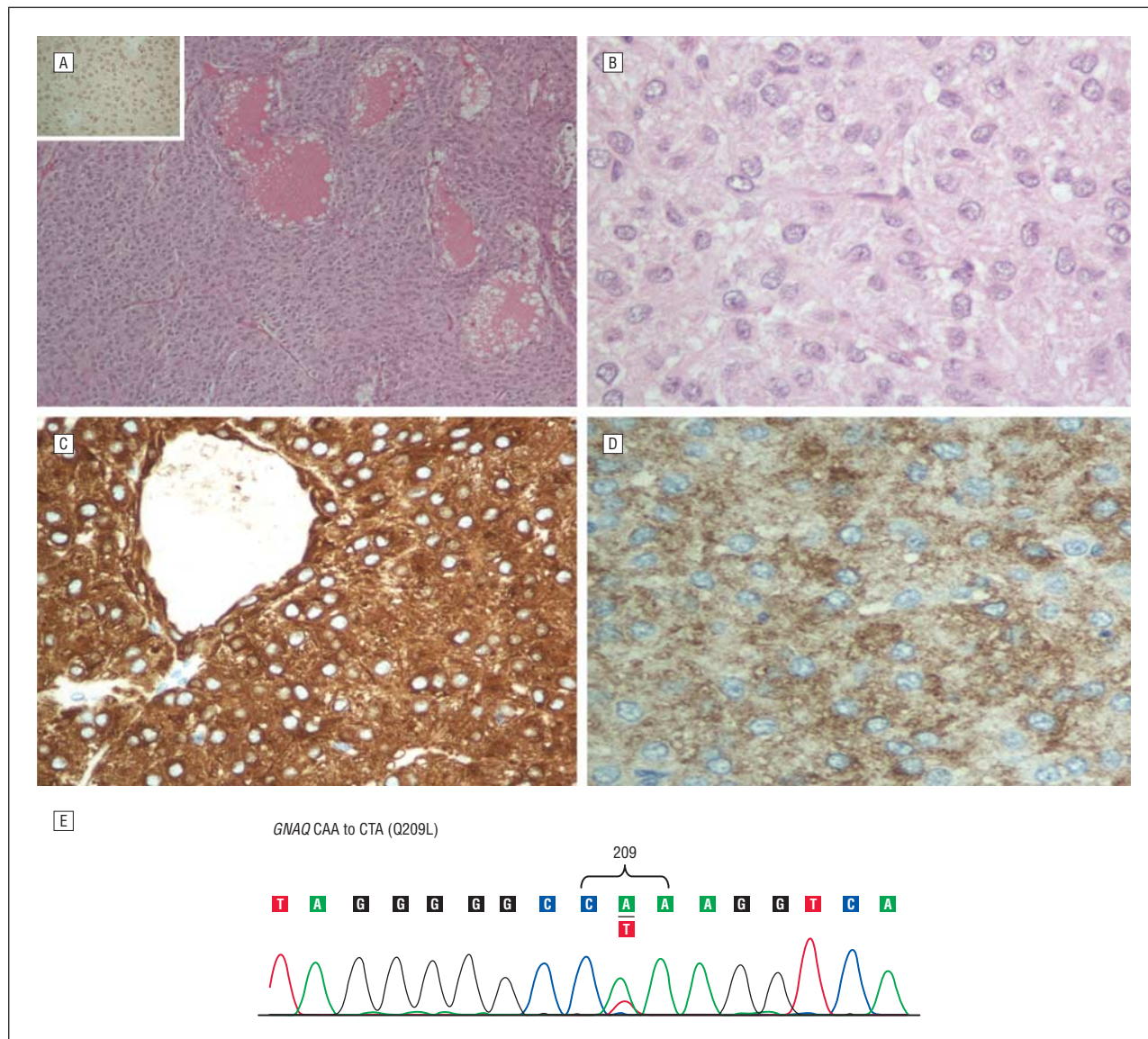


Figure 2. Histopathologic analysis and DNA sequence of *GNAQ*. **A**, Low-power photomicrograph shows regular polygonal-shaped cells with vascular spaces lined by tumor cells. Note the low nuclear to cytoplasmic ratio with vesicular nuclei, indistinct nucleoli, and lack of mitoses (hematoxylin-eosin, original magnification $\times 100$). Inset, Scant melanin pigmentation is visible on Fontana-Masson staining (original magnification $\times 400$). **B**, High-power photomicrograph shows the low nuclear to cytoplasmic ratio with vesicular nuclei, indistinct nucleoli, and lack of mitoses (hematoxylin-eosin, original magnification $\times 400$). **C**, The melanoma stains strongly for Melan-A (avidin-biotin immunoperoxidase, hematoxylin counterstain, original magnification $\times 400$). **D**, It also stains strongly for HMB-45 and S-100 protein (not shown) (avidin-biotin immunoperoxidase, hematoxylin counterstain, original magnification $\times 400$). **E**, The DNA sequence shows the heterozygous CAA to CTA mutation in exon 5 of *GNAQ*, causing substitution of glutamine by leucine.

made and enucleation was performed. The left eye was normal.

At enucleation, the globe had a bulge of the sclera in the posterior, superotemporal quadrant overlying the mass. It was opened to obtain fresh tissue for genetic testing. Grossly the mass was atypical for retinoblastoma, forming a solid, cream-colored, amelanotic tumor (Figure 1D).

Microscopically, a dome-shaped tumor measuring 13 mm in diameter and 10 mm in height arose in the posterior choroid. The tumor cells were large and polygonal with fibrillar eosinophilic cytoplasm and a low nuclear to cytoplasmic ratio (Figure 2A and B). Very occasional melanin granules were present, confirmed by Fontana-Masson staining (Figure 2A, inset). Nuclei were ve-

sicular without prominent nucleoli or mitotic figures. Small vessels were present, as were large vascular spaces lined by tumor cells. There was no extrascleral extension. The optic nerve was not involved.

Immunohistochemistry showed strong positive staining for Melan-A, HMB-45, and S-100 protein (Figure 2C and D). The Ki-67 rate was less than 1%. The following stains were negative: muscle actin, desmin, caldesmon, keratin, glial fibrillary acidic protein, neurofilament, synaptophysin, and chromogranin. Although not characteristic histologically, we made a tentative diagnosis of choroidal melanoma. To confirm the diagnosis, the tumor was sequenced for *GNAQ* and *GNA11* mutations; a Q209 CAA to CTA mutation was found in exon 5 of *GNAQ* (Figure 2E).

Findings on a full-body workup were negative, giving a final classification of T3aN0M0, stage IIB. No adjuvant treatment was given. Two years later, the patient has no evidence of recurrence or metastasis.

Comment. Uveal melanoma in children younger than 10 years is extremely rare, representing only 0.12% of all UMs.¹ To our knowledge, only 5 cases of congenital UM have been reported.² We believe our case may be congenital given the history of abnormal pupillary reflex noted at 6 months.

The clinical and histopathologic features of pediatric UM are usually similar to those found in adults.³ They are typically unilateral, occur in the choroid with no sex predilection, and are usually of spindle cell type.¹ Predisposing conditions associated with pediatric UM have included ocular melanocytosis, neurofibromatosis type 1, familial melanoma, and cutaneous dysplastic nevus syndrome, none of which were found in our patient.³ In the largest series, which had a median follow-up of 51 months, 4 of 63 patients died of metastatic disease and the 15-year survival was 0.77 (95% CI, 0.52-1.00), similar to that in adults.¹

Although immunohistochemical staining confirmed a melanocytic lesion, the atypical histopathologic features of the tumor and the age of the patient made the diagnosis of choroidal melanoma uncertain. To confirm the diagnosis, a *GNAQ* and *GNA11* somatic mutation analysis was performed. Van Raamsdonk et al⁴ found that 83% of UMs have a somatic mutation in either *GNAQ* or *GNA11*. The Q209 mutation prevents guanosine triphosphatase activity and locks the α subunit in a guanosine triphosphate-bound active state. This upregulates the mitogen-activated protein kinase pathway, a major contributor to cell proliferation in melanocytic neoplasms.^{4,5}

Given the paucity of pediatric UMs, prognostic factors and outcomes remain poorly known. In this case, the Ki-67 index was low and there was no extraocular extension, so we believe that the tumor is less likely to be aggressive.

To our knowledge, this is the first reported case in which a *GNAQ* oncogenic mutation has been demonstrated in a presumed case of congenital UM. This marker may serve as an additional helpful diagnostic tool for unusual uveal melanocytic tumors.

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Mutational Analysis of *GNAQ* and *GNA11* to Aid Therapy Management of a Choroidal Melanoma Metastatic to the Contralateral Orbit

Metastasis to the contralateral orbital cavity in uveal melanoma (UM) is extremely rare.¹ Only 8 cases of such metastases have been reported, and none included mutational analysis. For the first time, to our knowledge, we report data from a mutational analysis of *GNAQ* and *GNA11* supporting the diagnosis of a single metastatic tumor.

Report of a Case. A 53-year-old man had right-sided retrobulbar pain persisting for 4 weeks. The patient had undergone enucleation of his left eye 3 years previously for choroidal melanoma (27 × 12 × 10 mm). At this time, no other malignant neoplasms were observed by chest radiography, abdominal ultrasonography, and dermatological examinations. Findings on yearly magnetic resonance imaging of the orbital cavities with a T2-weighted turbo spin-echo sequence were unremarkable until 12 months prior to presentation (**Figure 1A**). Visual acuity of the remaining eye was 20/20. Findings on further ophthalmological examinations were normal. No periorbital hyperpigmentation or axial proptosis was present. An axial T2-weighted turbo spin-echo sequence magnetic resonance image demonstrated a right-sided, upper intraconal, hypointense lesion (20 × 11 × 12 mm) (**Figure 1B**).

A brown-colored tissue sample (10 × 10 mm) without pigmentation of the unaffected orbital tissue was obtained by performing a biopsy via the transcutaneous medial orbitotomy route. Histological analysis revealed weakly pigmented epithelioid cells and strongly pigmented spindle cells, leading to the diagnosis of melanoma (**Figure 2A**). An increased mitotic count (>5/10 high-power fields) and no connective tissue loops were observed. Immunohistochemical staining demonstrated tumor cells positive for S-100 protein and HMB-45, while Ki-67 (MIB-1) showed a growth fraction of 20% (data not shown).

For molecular karyotyping, array comparative genomic hybridization using the Agilent Technologies platform was performed according to the manufacturer's instructions. It revealed loss of chromosome 3, partial loss of 1p, 2q33-qter, 6q, and 16q, and gain of 8q and 16p.