TRAF7 somatic mosaicism in a patient with bilateral optic nerve sheath meningiomas: illustrative case

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BACKGROUND In the past decade, next-generation sequencing has spurred significant progress in the understanding of cytogenetic alterations that occur in meningiomas. Eighty percent of adult meningiomas harbor pathogenic somatic variants involving NF2, TRAF7, SMARCB1, KLF4, PI3K, or POLR2A. Somatic variants in TRAF7 associated with meningiomas usually localize to the gene’s WD40 domains but are mutually exclusive to germline mutations, which cause a distinctive autosomal dominant syndrome.

OBSERVATIONS This case involved a 15-year-old girl with bilateral optic nerve sheath meningiomas, diffuse meningiomatosis, and syndromic features, including craniosynostosis, brain anomalies, syndactyly, brachydactyly, epicanthus, and patent ductus arteriosus. Genetic testing of the meningioma specimen 7 years after biopsy showed a pathogenic p.R641C variant within the WD40 domain of the TRAF7 gene. Additional testing of unaffected tissues identified the same variant at lower allele frequencies, consistent with postzygotic somatic mosaicism.

LESSONS The authors report postzygotic somatic mosaicism for a p.R641C variant in the TRAF7 gene in a patient with bilateral optic nerve sheath meningiomas, diffuse meningiomatosis and a constellation of systemic findings previously recognized in patients with germline mutations of this gene. This is the first report of optic nerve sheath meningioma in a patient with mutation in the TRAF7 gene.

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KEYWORDS WD40 domain; p.R641C; meningiomatosis; craniosynostosis; TRAF7 syndrome; mosaicism
Here we report a child with diffuse meningiomatosis leading to development of bilateral optic nerve sheath meningiomas. Next-generation sequencing of tumor tissue showed a pathogenic mutation in TRAF7. No prior study has found any gene, other than NF2, mutated in bilateral optic nerve sheath meningiomas. Analysis of other tissues revealed the presence of the same mutant allele at a low frequency. Review of the patient’s history uncovered systemic features heretofore only described in germline TRAF7 syndrome.

**Illustrative Case**

A 15-year-old girl was referred to the neuroophthalmology clinic by an optometrist who had observed bilateral optic disc swelling. The patient reported a recent history of declining vision and new onset of headache. The child’s parents were of European ancestry. The patient had second–third toe syndactyly and first–fourth/fifth toe brachydactyly. Facial features were significant for epicanthal folds and a low hairline. There was a history of postnatal surgical repair of a patent ductus arteriosus.

On examination, visual acuity was 20/40 in the right eye and 20/100 in the left eye. The pupillary reflexes were normal. No Marcus Gunn pupil was present. Extraocular eye movements were full. Humphrey threshold visual field tests revealed severe depression in both eyes (Fig. 1A and B). Slit-lamp examination was unremarkable, and intraocular pressure was normal. Dilated fundus examination revealed bilateral optic disc swelling (Fig. 1C and D). Certain features suggested chronicity, such as pallor and pseudodrusen. Cranial examination was notable for scaphocephaly with frontal bossing. Neurological examination, including the cranial nerves, was otherwise unremarkable. The patient was a high school student with average scholastic ability.

![FIG. 1. Humphrey visual field tests and fundus photography at presentation. A and B: Thirty-degree threshold visual field tests showing severe depression in both eyes. C and D: Fundus photographs showing bilateral optic disc swelling with pallor and pseudodrusen.](image)

![FIG. 2. Head and brain anomalies. A: Three-dimensional reconstruction computed tomography (CT) demonstrating absence of the sagittal suture with scaphocephaly. B: Noncontrast sagittal MRI showing small posterior fossa, platybasia, cerebellar tonsillar herniation (black arrow), narrow foramen magnum, hypoplasia of the posterior corpus callosum, and pronounced enlargement of the sella turcica (white arrow) with an elongated pituitary stalk and partially empty appearance. C: Noncontrast sagittal CT showing calcification along the inferior border of the falx cerebri (arrows) and at its junction with the tentorium.](image)
Neuroimaging revealed extensive, previously undiagnosed developmental anomalies. There was absence of the sagittal suture with resulting scaphocephaly on three-dimensional reconstruction computed tomography (Fig. 2A). Noncontrast magnetic resonance imaging (MRI) showed a constellation of abnormalities, including a small posterior fossa, platybasia, cerebellar tonsillar hemiation, narrow foramen magnum, hypoplasia of the posterior corpus callosum, and pronounced enlargement of the sella turcica with an elongated pituitary stalk and partially empty appearance (Fig. 2B). Calcification was present along the inferior border of the falx cerebri and at its junction with the tentorium (Fig. 2C).

Postgadolinium MRI disclosed diffuse nodular thickening of the leptomeninges extending bilaterally from the cerebellopontine angles through the foramen magnum and encasing the brainstem (Fig. 3A). Noncontrast magnetic resonance imaging (MRI) showed a constellation of abnormalities, including a small posterior fossa, platybasia, cerebellar tonsillar hemiation, narrow foramen magnum, hypoplasia of the posterior corpus callosum, and pronounced enlargement of the sella turcica with an elongated pituitary stalk and partially empty appearance (Fig. 2B). Calcification was present along the inferior border of the falx cerebri and at its junction with the tentorium (Fig. 2C).

Postgadolinium MRI disclosed diffuse nodular thickening of the leptomeninges extending bilaterally from the cerebellopontine angles down through the foramen magnum (Fig. 3). The contrast-enhancing mass encased the brainstem. There was thickening and enhancement of the petroclival ligaments, caverno-apical triangles, and tuberculum sellae. The abnormal dural enhancement extended through the optic canals to involve both optic nerve sheaths. There was a classic “tram track” sign, associated with optic nerve sheath meningioma (Fig. 4A). Coronal images showed a typical appearance for optic nerve sheath meningiomas (Fig. 4B).
The appearance of these lesions on MRI was concerning for neoplastic disease. A diffuse pachymeningeal process such as diffuse meningiomatosis was suspected, given the extent of dural calcification that correlated with enhancing lesions on MRI.

Blood tests and cerebrospinal fluid analysis were negative for an infectious, inflammatory, or neoplastic process. A suboccipital decompression was performed with biopsy of the enhancing dural-based lesion at the craniocervical junction. Histopathological examination of the specimen showed meningotheilial cells arranged in whorls associated with psammomma bodies are also present. Chart shows TRAF7 p.R641C variant allele encountered in formalin-fixed pathology specimens (meningioma, skull) and in fresh samples (buccal mucosa, pathology). H&E stain, original magnification ×100.

FIG. 5. Meningioma biopsy specimen and TRAF7 p.R641C mutation. Numerous small whorls of meningotheilial cells are seen without significant nuclear atypia, consistent with a World Health Organization grade I meningothelial meningioma. Scattered psammoma bodies are also present. Chart shows TRAF7 p.R641C variant allele encountered in formalin-fixed pathology specimens (meningioma, skull) and in fresh samples (buccal mucosa, pathology). H&E stain, original magnification ×100.

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tumor necrosis factor signaling, immune response pathways, cellular differentiation, and apoptosis.\textsuperscript{16,18} TRAF7 mutations associated with meningioma are localized to the WD40 domains, suggesting that molecular interactions with this region of the protein play an important role in tumorigenesis.\textsuperscript{6,16} TRAF7 is involved in p53, MEKK3, nuclear factor-xB and ubiquitination pathways, which are key regulators of tumor development.\textsuperscript{16,18} In addition, meningiomas with TRAF7 mutations overexpress the checkpoint inhibitors programmed death-ligand 1 (PD-L1), indoleamine 2,3-dioxygenase (IDO), and tryptophan 2,3-dioxygenase (TDO2), impeding the ability of immune cells to migrate into a tumor site.\textsuperscript{19}

**TRAF7 Syndrome**

Nearly a decade after the role of TRAF7 somatic mutation was identified in meningioma formation, a distinct germline TRAF7 syndrome was recognized. It is characterized by abnormal facies, skeletal and cardiac defects, and developmental delay.\textsuperscript{20,21} Most reported cases involve missense mutations within the WD40 domains of TRAF7.\textsuperscript{21} Three TRAF7 variants involving the coiled-coil domain (rather than WD40 repeats) have also been identified; however, patients with these variants did not always present with the same characteristic facies.\textsuperscript{21} In nearly all cases, the germline variant arises de novo.\textsuperscript{7,18}

Only a single prior case of postzygotic somatic mosaicism of a pathogenic TRAF7 mutation has been described.\textsuperscript{20} The patient (subject #7) harbored a mutation in the coiled-coil domain. The mosaic phenotype in this patient was just as severe as that found in other patients with germline mutations.

Our patient had multiple congenital anomalies described in TRAF7 syndrome, including patent ductus arteriosus, brain anomalies, craniosynostosis, abnormal facies, and digital anomalies. However, she did not have intellectual disability, a feature that is present in all other reported cases of TRAF7 syndrome.\textsuperscript{20,21} Testing excluded a germline TRAF7 mutation. However, multiple uninvolved tissues (saliva, buccal swab, skull, blood) tested at different times identified a p.R641C variant located in the WD40 domain of TRAF7. This particular variant has not previously been reported in patients with germline or mosaic mutations in TRAF7.

Curiously, the variants reported to cause germline TRAF7 syndrome have so far been mutually exclusive from the somatic mutations that occur in meningioma.\textsuperscript{21} Moreover, meningioma has been reported in only a single patient with germline TRAF7 syndrome.\textsuperscript{20} The distinct phenotypes seen in germline versus somatic mutations may reflect differences in the activity of the mutant TRAF7 protein with respect to its downstream roles in tumorigenesis and signal transduction. Most meningiomas with mutations in TRAF7 also harbor a second pathogenic variant,\textsuperscript{6} which implies that there are limited loci that can independently promote tumor formation. Little is known about the direct role of the TRAF7 protein in the various developmental anomalies seen in TRAF7 syndrome, although downstream MEKK3 pathways are thought to be important in cardiac and craniofacial development.\textsuperscript{22} Further study of TRAF7 pathways and their role in normal development and disease is required to better understand the effects of alterations at the specific loci associated with both meningioma and TRAF7 syndrome.

**TRAF7 Variants in Meningiomas**

Recent studies have uncovered the genetic landscape of adult meningioma.\textsuperscript{6–10} A somatic TRAF7 mutation is present in 20% of adult meningiomas.\textsuperscript{6} Approximately 75% of these cases manifest an additional mutation in KLF4, AKT1, or PIK3CA genes.\textsuperscript{6} Interestingly, it is rare to find concomitant mutations in TRAF7 and NF2.\textsuperscript{6–10} Our patient was negative for any other gene mutation reported in meningioma. Her mutation at the R641C locus has been reported in 4% of meningiomas with TRAF7 gene mutations.\textsuperscript{6}

For pediatric meningioma, the molecular pathogenesis has been less well established. Battu et al. evaluated specimens from 36 children with sporadic meningioma and found 72% of cases positive for 22q deletion, 16% with combined 1p and 14q deletion, and 8% with isolated 1p deletion.\textsuperscript{21} They identified no cases with a mutation in AKT, SMO, KLF4, TRAF7, or pTERT, which are present in adult meningiomas.\textsuperscript{23} A second study cataloged genetic abnormalities in 38 pediatric meningiomas and reported 68% showing somatic loss-of-function mutations in NF2 or chromosome 22 loss.\textsuperscript{24} This study identified pathogenic variants in four cases, including SMARCQ1, FUBP1, BRAF, pTERT, CHEK2, SMAD, and GATA4. No cases of TRAF7 mutation were reported.\textsuperscript{24} These two studies suggest that genetic findings in adult and pediatric meningioma differ. Although prior to our case no TRAF7 mutation had been reported in a pediatric patient with meningioma, it is difficult to evaluate this finding given the limited data published about meningioma within the postpubertal age group. It is possible that the molecular pathogenesis of meningiomas arising in adolescent patients is more concordant with that seen in adult patients.

**Optic Nerve Sheath Meningiomas**

There is only a single case previously reported of bilateral optic nerve sheath meningioma in a child.\textsuperscript{25} Patients with optic nerve sheath meningiomas rarely undergo resection or incisional biopsy because the diagnosis can usually be made via neuroimaging and surgery carries a high risk of vision loss.\textsuperscript{26} Consequently, there are limited data regarding the molecular pathogenesis of isolated optic nerve sheath meningiomas. A notable study showed chromosome 22q loss in 10/14 patients with orbital meningioma but only 1/5 with optic nerve sheath meningioma.\textsuperscript{27} Another molecular change included copy number alternations involving chromosome 2.\textsuperscript{27} There have been no prior reports of a gene mutation in TRAF7 in a primary optic nerve sheath meningioma specimen. It must be noted that the specimens collected in our patient were from meningioma at the craniofacial junction, not the optic nerve sheaths. However, the tumor extended continuously from the biopsy site up the skull base and through the optic canals into the orbits. The detection of a somatic variant known to cause meningioma supports the inference that it was also present in the patient’s optic nerve sheath meningiomas.

**Lessons**

We report a case of postzygotic somatic mosaicism of the TRAF7 p.R641C variant in a patient with bilateral optic nerve sheath meningioma, diffuse meningiomatosis, and some features of TRAF7 syndrome. TRAF7 germline mutations cause an autosomal dominant syndrome with mutations frequently localizing to the WD40 domains but mutually exclusive to WD40 somatic variants found in meningiomas. The mosaic p.R641C variant identified in this case has not been reported previously in a patient with a germline or mosaic mutation in TRAF7.
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Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions
Conception and design: Horton, Kaidonis, Van Ziffle. Acquisition of data: all authors. Analysis and interpretation of data: Horton, Kaidonis, Pekmezci, Van Ziffle. Drafting the article: Horton, Kaidonis, Van Ziffle. Critically revising the article: Horton, Kaidonis, Pekmezci, Van Ziffle. Reviewed submitted version of manuscript: Horton, Kaidonis, Pekmezci, Auguste. Approved the final version of the manuscript on behalf of all authors: Horton. Statistical analysis: Kaidonis. Administrative/technical/ material support: Horton, Kaidonis, Pekmezci. Study supervision: Horton.

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