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# Intraocular Teratoma in a Mouse

**Richard S. Smith, MD, DMedSci,[1,2*] James V. Miller,[1] and John P. Sundberg, DVM, PhD[1]**

**A 4.5-month-old male B6.129S2-*Trp53*$^{tm1Tyj}$ mouse developed an enlarged left eye. After euthanasia, the eye was removed and found to contain a teratoma composed of smooth muscle, white fat, neural tissue, and villous intestinal epithelium with appearance similar to that of the small intestine. Many normal intraocular structures were absent. To our knowledge, this represents the first reported intraocular teratoma in a mouse.**

The term hamartoma (grossly visible proliferation of normal tissue in its normal location) applies to common spontaneous human lesions such as nevi and cutaneous hemangiomas. Spontaneous hamartomas have been reported in mice (1, 2), but are most often the product of genetic engineering. (3, 4). Choristomas (grossly visible proliferation of normal tissues in an abnormal location) are uncommon in all animals, including humans (5) and laboratory mice (6). Teratomas are usually defined as cellular proliferations that include all three germ layers, and may appear as either developmental abnormalities or true neoplasms (5). Hamartomas, choristomas, and teratomas may affect the orbit and ocular adnexae, but rarely develop as intraocular lesions (7-10).

## Case Report

During routine colony screenings, a 4.5-month-old male B6.129S2-*Trp53*$^{tm1Tyj}$ (homozygous for a targeted mutation of the *Trpp53* gene and deficient in its product (11), hereafter referred to as p53$^{-/-}$) mutant laboratory mouse was submitted with an enlarged left eye that was 4 mm in diameter, whereas the normal right eye was 3 mm in diameter. The mouse was euthanized because of the risk of infection and the possibility that the eye contained a tumor.

## Methods

All mice of the colony in which this mouse was discovered are cared for and used humanely according to the AALAS "Policy on the Humane Care and Use of Laboratory Animals" and under a protocol approved by the Institutional Animal Care and Use Committee of the Jackson Laboratory. After $CO_2$-induced euthanasia, the skull containing both eyes was collected and fixed overnight in Fekete's acid-alcohol-formalin, transferred into 70% ethanol, processed in routine manner, and embedded in paraffin (12). After routine histologic evaluation, the block was serially sectioned at 6-µm thickness, and every fifth section was stained with hematoxylin and eosin (H&E). Additional sections were stained with Masson's trichrome, alcian blue, and periodic acid Schiff (13). Adjacent sections were processed for immunohistochemical analysis according to the manufacturers protocols for smooth muscle actin (Sigma Chemical Co., St. Louis, Mo.) and glial fibrillary acidic protein (GFAP) (Dako, Carpinteria, Calif.) to identify the cellular components of the tumor (14).

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*[1]The Jackson Laboratory, 600 Main Street, Bar Harbor, Maine and [2]The Howard Hughes Medical Institute.*
*[*]Corresponding author.*

## Results

The right eye was normal. The left eye was severely malformed. The cornea was normal except for minimal peripheral vascularization, and the sclera was normal. The anterior chamber, trabecular meshwork, iris, and ciliary body were all absent, although a few pigmented cells were present in the tissue that replaced the anterior chamber. The posterior portion of the cornea was lined with eosinophilic tissue, much of which strongly expressed smooth muscle actin epitopes (Fig. 1). In the early serial sections, lens cortex, lens capsule, and proliferating lens epithelium were clearly identified even though lens formation was incomplete. Internal to the abnormal smooth muscle and lens remnants, the entire globe was lined by columnar epithelium with a microvillous border interspersed with goblet cells. The lining epithelium was located on a lamina propria and resembled small intestine. In some anterior locations there were cellular aggregations that resembled small intestinal crypts. Large focal accumulations of lymphocytes, resembling Peyer's patches, were evident beneath the intestinal epithelium. The goblet cells were strongly positive to PAS and alcian blue stains (Fig. 2). The inner cavity of the eye, normally filled with the lens and the acellular vitreous, contained free melanin granules, neutrophilic leukocytes, desquamated intestinal lining cells, and alcian blue-positive material (presumably mucin).

In the posterior segment of the globe, normal choroidal tissue was present. At some levels of section, retinal pigment epithelium was identified, and adjacent tissue with a lamellar cell arrangement was likely incompletely differentiated retina, although the tissue did not express GFAP. In some locations, the malformed retina was separated from the intestinal tissue by normal white fat (Fig. 3). In two locations that lacked any retinal tissue, there were dense deposits between the choroid and intestinal epithelium of eosinophilic, strongly GFAP-positive material suggesting neural tissue.

## Discussion

A spontaneous intraocular lesion was identified in a B6.129S2-*Trp53*$^{tm1Tyj}$ mutant mouse. A wide variety of tissues were observed, including smooth muscle, white fat, neural tissue, and villous intestinal epithelium with appearance similar to that of the small intestine. Most of the abnormal tissues were

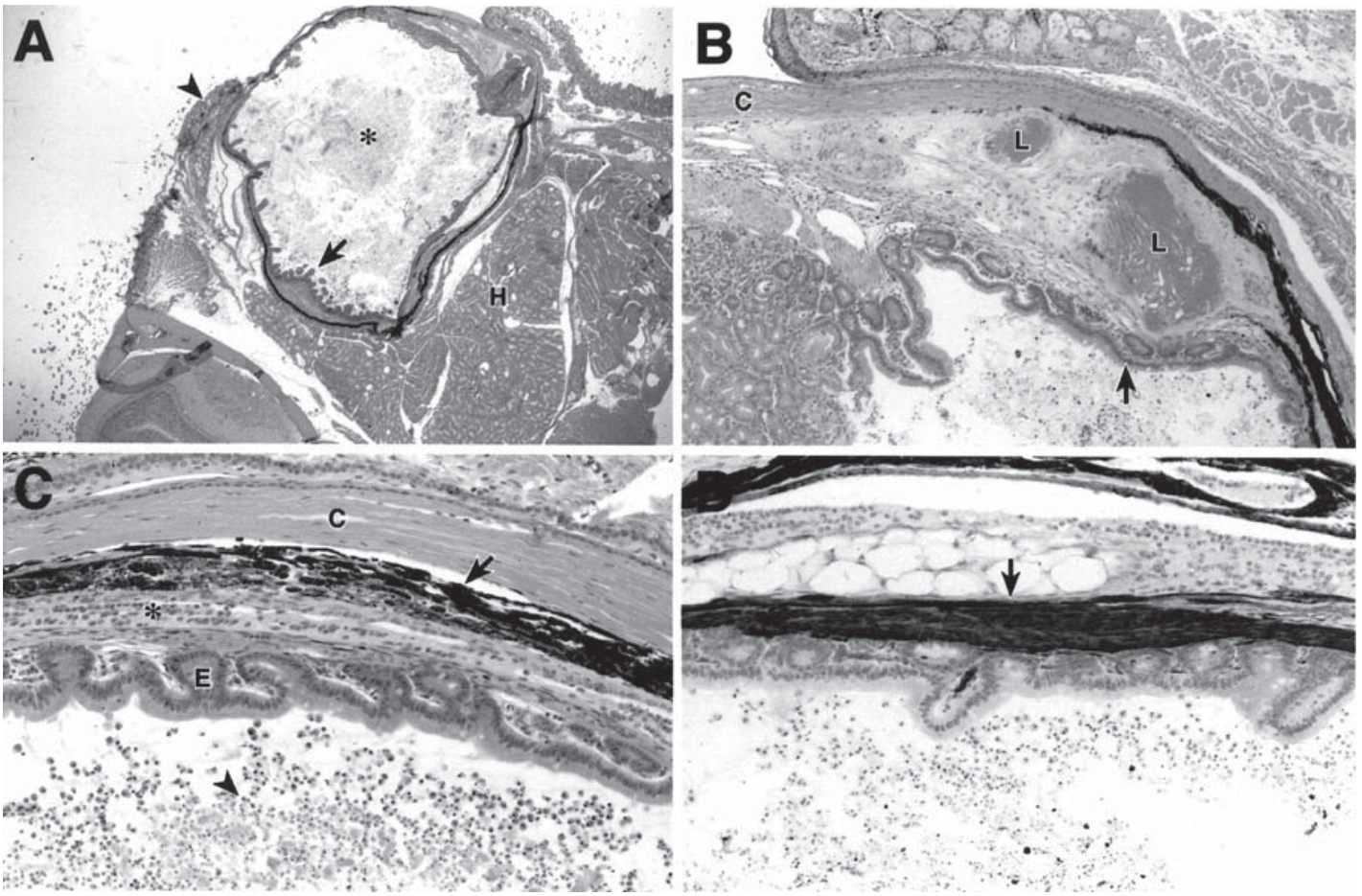


**Figure 1.** Photomicrographs of sections of the affected eye of the mouse of this report.
(A) Normal intraocular structures are absent. The globe is filled (asterisk) with cellular debris and amorphous eosinophilic material. The lids (arrowhead) and Harderian gland [H] are normal. Arrow indicates the intestinal epithelial lining of the teratoma. H&E stain; original magnification, 20×
(B) There is some peripheral neovascularization of the cornea [C]. The anterior chamber is absent. Lens remnants [L] are enclosed in a cellular, eosinophilic tissue lined within the eye by villous columnar epithelium (arrow). H&E stain; original magnification, 100×.
(C) At higher magnification, a layer of pigmented tissue (arrow) is located directly beneath the cornea [C]. The pigmented tissue has none of the structural features of normal iris. Cellular eosinophilic tissue (asterisk) separates the pigmented tissue from the villous epithelium [E]. Necrotic cellular debris, neutrophils and free melanin pigment fill the interior of the eye (arrowhead). H&E stain; original magnification, 200×.
(D) In a nearby section, much of the eosinophilic tissue shown in C is strongly positive for smooth muscle actin (arrow); original magnification, 200×.

well differentiated without evidence of malignant change. Failure of formation or malformation of most intraocular structures was a prominent feature.

Because this lesion was found in a $p53^{-/-}$ mutant mouse, the possible role of *p53* in its genesis must be considered. It is known that $p53^{-/-}$ mice are prone to neoplasia (11). Of particular interest is the reported development of testicular teratomas in $p53^{-/-}$ mice on a mixed C57BL/6 and 129/Sv background (15). Initially reported as a tumor suppressor gene, *p53* also modulates gene transcription, acts to control the cell cycle, controls DNA repair, activates apoptosis, and stimulates neovascularization (11, 16-18). Absence of *p53* actually protects the eye from the increased incidence of microphthalmia, anophthalmia, and lens agenesis reported after genotoxic stress (17). Vitreal opacities, fibrous retrolental tissue, retinal folds, and optic nerve hypoplasia were reported in $p53^{-/-}$ mice on a C57BL/6J background (19). However, to our knowledge, previous reports of *p53*-deficiency-associated intraocular neoplasms or teratomas in mice have not been published.

Choristomas that involve the eye and ocular adnexae in humans are not rare. The most common types encountered are corneal dermoids and orbital dermoid cysts in children. Episcleral osseous choristomas, phakomatous choristomas, ectopic brain and lacrimal gland tissue, and choroidal osteomas are less common choristomatous lesions (8). Choristomas with heterotopic adipose tissue and smooth muscle associated with coloboma of the optic disk have been described (20).

The rare intraocular medulloepithelioma in children bears some resemblance to choristomas, since multiple tissue types are often present. In fact, the first such tumor, described by Verhoeff (7), was called a teratoneuroma. Those tumors often arise from the ciliary body and may reveal remarkable proliferation of non-pigmented ciliary epithelium in cords and tubules containing abundant hyaluronic acid. In addition, hyaline cartilage, brain tissue, and striated muscle are frequently identified (7). Medulloepitheliomas may be benign or malignant.

In mice, the predominant form of spontaneous choristoma consists of normal adipose tissue in the reticular dermis that

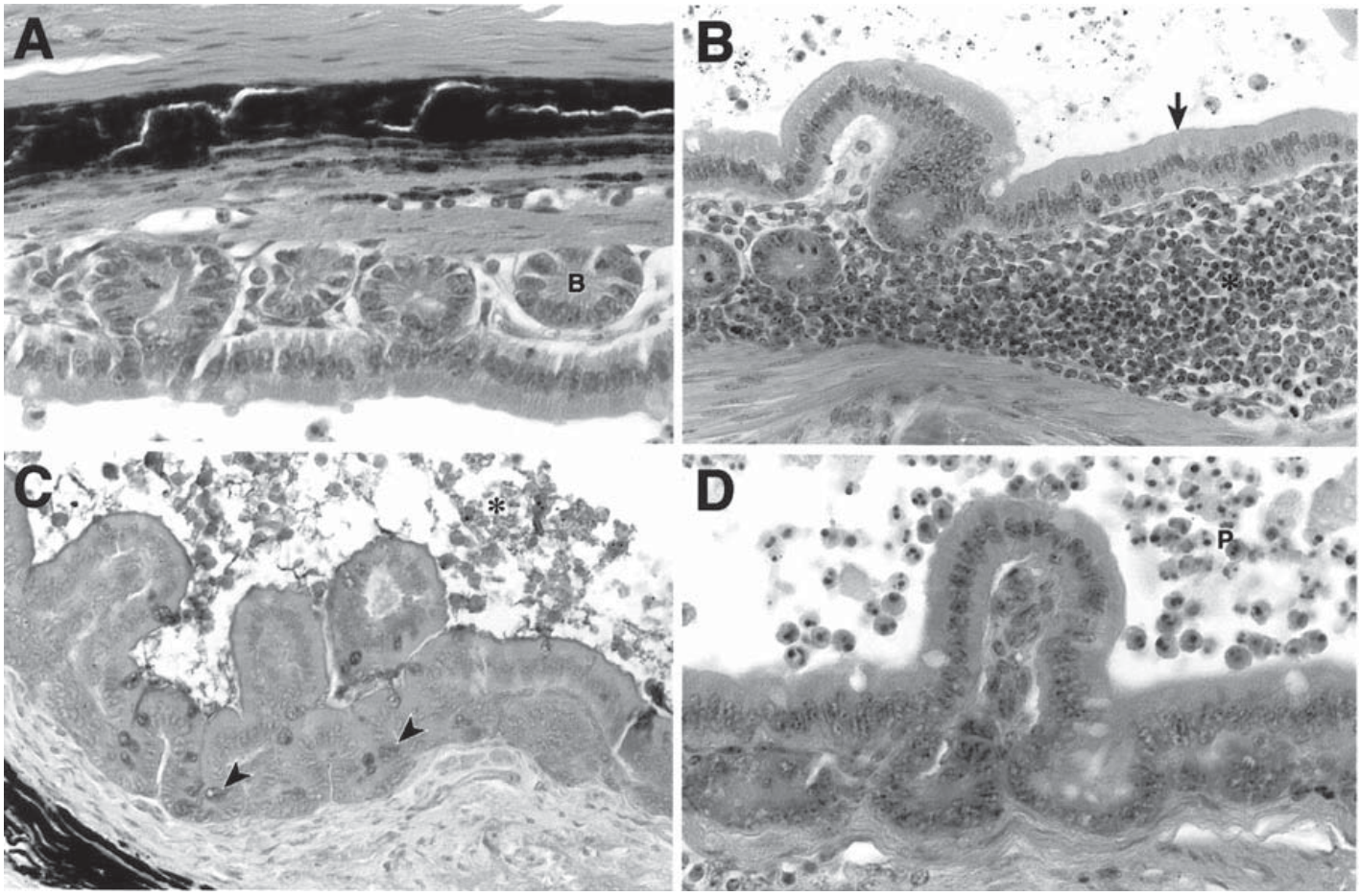


**Figure 2.** Photomicrographs of sections of the affected eye.
(A) In a section deeper than that in Figure 1, taken from a location adjacent to the cornea, adjacent to the columnar intestinal epithelium, are small glandular structures resembling small intestinal crypts. H&E stain; original magnification, 630×.
(B) The columnar nature of the epithelium and the basal location of the nuclei are apparent (arrow). Beneath the epithelium is a large collection of lymphocytes (asterisk) that resembles Peyer's patches. H&E stain; original magnification, 400×.
(C) There are abundant of goblet cells (arrowheads) in the intestinal epithelium, as well as large amounts of mucin present in the eye (asterisk). Alcian blue stain; original magnification, 400×.
(D) A dense infiltrate of neutrophils [P] is present inside the eye. H&E stain; original magnification, 630×.

occasionally extends through the skull sutures into the brain. Choristomas containing normal thyroid gland, intestine, respiratory epithelium, epithelial cysts, bone, and marrow, cartilage, and angiomatous lesions also were reported from a series of nearly 10,000 mice undergoing routine necropsy. The incidence of choristomas was low, varying from 0.24 to 6.2/100,000 depending on the strain (6). None of these choristomas involved the eye or ocular adnexae (21).

A teratoma is composed of a wide variety of tissues not normally present in the organ in which they are found. As such, a teratoma is a particular form of choristoma. Some authors define a teratoma as having representative tissue from at least two germ cell layers (5, 22), whereas others suggest that all three germ cell layers must be present (9). The intraocular teratoma in this mutant mouse consisted of intestinal epithelium and glands, smooth muscle, fat, and neural tissue. On the basis of these observations, we believe that all germ cell layers are represented and that the lesion in this mouse is properly termed a teratoma. To the best of our knowledge, this represents the first reported case of an intraocular teratoma in a mouse. Only two cases involving human eyes have been reported (9, 23).

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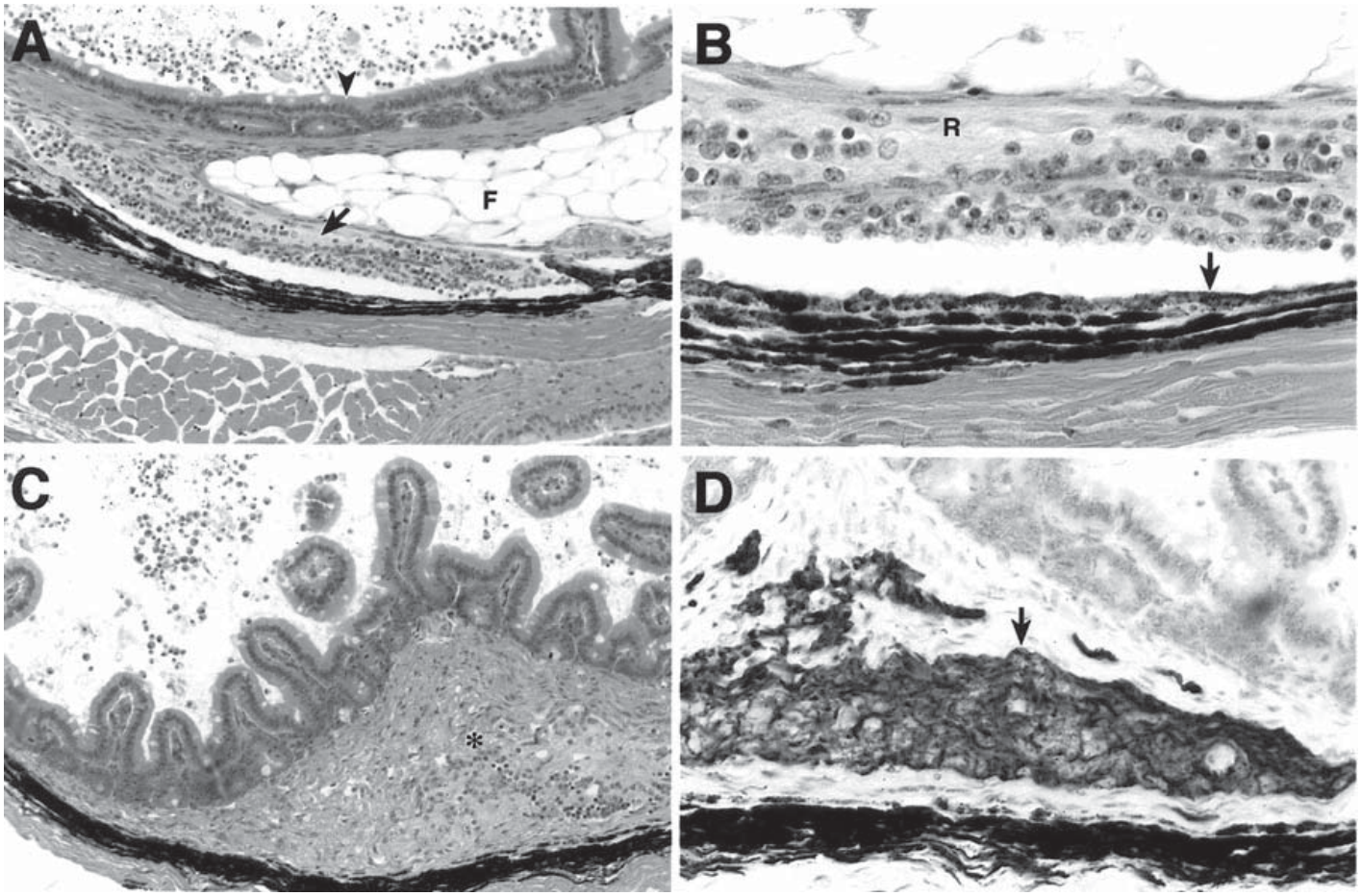


**Figure 3.** Photomicrographs of sections of the affected eye.
(A) In the posterior portion of the eye, intestinal-like epithelium (arrowhead) is often separated from more external tissue by a layer of normal white fat [F]. In this location, external to the fat is tissue with a poorly organized lamellar structure, representing retina (arrow). H&E stain; original magnification, 200×.
(B) At higher magnification, the malformed retina [R] lacks normal layers. Although not specifically identified, the nuclei resemble those of photoreceptors and retinal ganglion cells. The retina is artifactually separated from a small region that includes retinal pigment epithelium (arrow). H&E stain; original magnification, 630×.
(C) In the posterior portion of the eye, the villous epithelium is elevated by a mound of cellular eosinophilic tissue (asterisk), which did not react to smooth muscle actin. H&E stain; original magnification, 200×.
(D) The bulk of the eosinophilic tissue shown in C reacts strongly with an antibody to glial fibrillary acidic protein (GFAP; arrow). GFAP stain; original magnification, 400×.


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