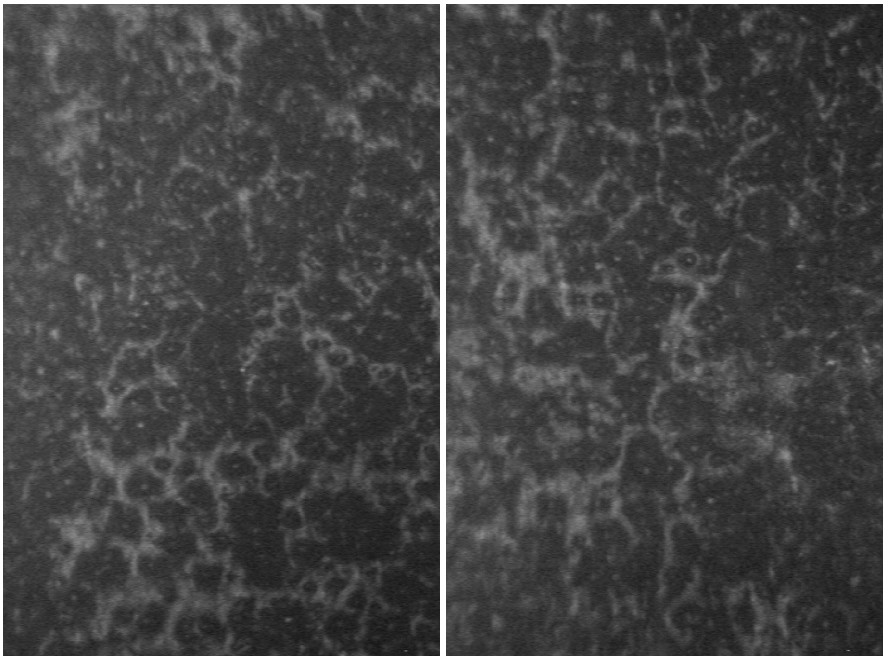


FUCHS. *Decreased cell density with abnormal cell morphology in both eyes of a female patient with Fuchs, seen via confocal microscopy. Thanks to a worldwide genotyping effort, researchers now have evidence of gender-specific risks.*

Variants at 4 Gene Loci Blamed for Fuchs Dystrophy

A MASSIVE GENOME-WIDE ASSOCIA-tion study has linked Fuchs endothelial corneal dystrophy (FECD) to faulty genes at 4 genetic loci, a finding that eventually could give affected families a way to determine which members are genetically predisposed to developing Fuchs later in life.[1]

Fuchs affects 4% of adults over age 40 and is the most common reason for corneal transplantation in the United States. Its heritability is estimated at 39%.

Worldwide effort. The scientists spent 12 years recruiting and genotyping 2,075 Fuchs patients and 3,342 controls at 16 research sites around the world. They also tested cornea tissue from eye banks and from patients undergoing transplantation. Analyses showed that genetic variations at the 4 loci predicted Fuchs cases with an accuracy of 78%, they wrote in *Nature Communications.*

"Previously, there was 1 known FECD locus. We've expanded that number to 4. These findings provide a deeper understanding of the pathology of FECD, which in turn will help us develop better therapies for treating or preventing this disabling disease," said Natalie A. Afshari, MD, at the University of California, San Diego.

Although these 3 new genetic loci were not previously linked to Fuchs or other corneal dystrophies, "in other organs and in animal models, they are known to have roles in several cellular processes," Dr. Afshari said. "They can affect a plasma membrane pump for water and ion transport, maintenance of cell membranes, tissue integrity, and cell-to-cell contact." She added, "Those are the kind of roles that the proteins encoded at these loci play in keeping the corneal endothelium healthy."

The researchers also confirmed the previously identified fourth locus, *TCF4* (transcription factor 4), which is involved in cellular replication.

Gender-related risks. In addition to suggesting possible mechanisms of disease pathogenesis, the researchers reported the first known gender-specific genetic risks for Fuchs. "We know that women are more affected by the disease than men. And here we found that the *LAMC1* variant [laminin gamma-1] confers higher risk among women, while the *TCF4* variant confers greater risk in men," Dr. Afshari said.

LAMC1 function is important because it has a role in normal basement membrane deposition, suggesting that the altered gene might lead to thickening of Descemet's membrane in Fuchs.[1]

The other 2 loci that the researchers linked to Fuchs were *ATP1B1*, which encodes a subunit of the sodium-potassium plasma membrane pump, and *KANK4* (KN motif- and ankyrin repeat domain-containing protein), which might help regulate actin stress fibers, Dr. Afshari said. *KANK* proteins are thought to hold endothelial cell nuclei in place through cellular adhesion of the endothelial cytoplasmic layer.[1]

It will take further studies to understand how the 4 gene loci impact heritability, disease onset, and progression rates in Fuchs families, Dr. Afshari said. But the research might eventually lead

to screening tests or even to gene-based therapies, she said. "Family members who have Fuchs are concerned about the risk for their children and, especially, their grandchildren. I tell them, 'By the time your grandchildren are affected—and probably much sooner—we will likely be doing genetic corrections.'"

—Linda Roach

1 Afshari NA et al. *Nat Commun.* 2017;8:14898. doi:10.1098/ncomms14898.

Relevant financial disclosures—Dr. Afshari: None.

RETINA

Autophagy Protects Ocular Cells From Dye Toxicity

INDOCYANINE GREEN (ICG) AND brilliant blue G (BBG) are 2 vital dyes commonly used to highlight and help remove the internal limiting membrane (ILM) during vitreoretinal surgery. However, researchers have found them toxic to both retinal pigment epithelium and photoreceptor cells. Now, researchers in Taiwain have reported that autophagy—a process occurring in cells in response to oxidative stress—may play a role in protecting some types of ocular cells when exposed to these dyes.[1]

Autophagy's role. In the study, genetic and pharmacological ablation of autophagy worsened cytotoxicity of ICG and BBG in mouse ocular cells, indicating that autophagy might act as a survival mechanism in ocular cells exposed to the dyes. Use of dietary supplements—such as resveratrol, lutein, and coenzyme Q_{10} (CoQ_{10})—induced autophagy, reducing the dyes' cytotoxic effects.

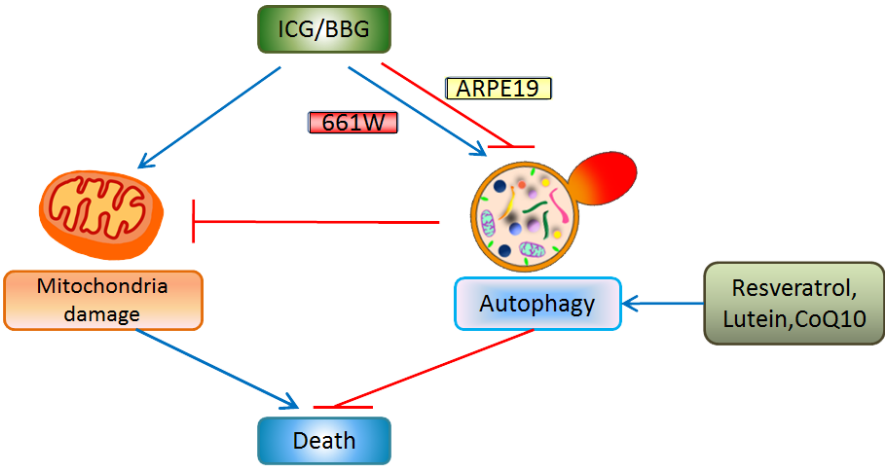
The results suggest that it is prudent to protect the hole area during staining, said lead researcher Shwu-Jiuan Sheu, MD, at the Kaohsiung Veterans Hospital in Kaohsiung, Taiwan. "This is especially true in macular hole retinal detachment, which allows more direct contact between the dye and photoreceptors," she said. "Low doses and short exposure times remain critical during chromovitrectomy."

Although the researchers found that dietary supplements may play a protective role by boosting autophagy, Dr. Sheu said it was premature to suggest their use for this purpose. "It would be more practical to develop a local agent to help protect against these dyes," she said. An autophagy inducer might be used in a similar way as rapamycin is used to protect cardiac cells during ischemia/reperfusion injury.

—Annie Stuart

1 Sheu S-J et al. *PLoS ONE.* 2017;12(3):e0174736. doi:10.1371/journal.pone.0174736.

Relevant financial disclosures—Dr. Sheu: This work was supported by Kaohsiung Veterans General Hospital and the Ministry of Science and Technology in Taiwan.



PROTECTIVE? *Autophagy modulation may be able to prevent the damage caused by vital dyes (ARPE-19 = RPE cells; 661W = photoreceptor cells).*

CATARACT

Rethinking Radiation Doses for Eye Protection

A PANEL OF RADIATION PROTECTION experts has recommended a significant drop in the annual, occupational dose of ionizing radiation permissible for the crystalline lens.

The goal: to reduce the incidence of radiation-induced cataracts.

After an extensive review on behalf of the National Council for Radiation Protection and Measurements (NCRP), the scientists recommended cutting the maximum occupational dose to the lens by two-thirds, to 50 millisieverts (mSv) annually.[1] (On average, Americans receive about 6 mSv of radiation per year from naturally occurring and medical exposures.)

Protecting patients. For ophthalmologists, this stricter standard suggests that a new level of vigilance should be employed for certain patients, notably medical colleagues whose work involves radiation, said the panel's cochair, Lawrence T. Dauer, PhD, at Memorial Sloan Kettering Cancer Center in New York City. Such colleagues would include interventional cardiologists and radiologists, Dr. Dauer said.

Assessing the evidence. The panel noted that there has been a gradual realization in recent years that radiation-induced cataracts can occur at much lower, chronic dose levels than was previously thought. Dr. Dauer said the group evaluated nearly 60 epidemiological studies and found evidence (albeit weak) of causation at low doses and at low dose-rates of radiation exposure.

"We recognized that there likely were effects at doses lower than previously understood and therefore felt it was prudent to reduce the limit, rather than leave it where it was," he said. "We thought that a reduction in the limit for the eye could wake up some of the radiation protection community to recognize the lens as a potential issue, about which we should be more concerned than we have been in the past."

Shwu-Jiuan Sheu, MD

ALZHEIMER DISEASE

Retinal Scan for Early Dx of Alzheimer?

THE RETINAL ARTERIOLAR CENTRAL REFLEX (CR) may provide information about microvascular health in the retina and the brain. And according to researchers in Australia, it adds to previous findings on retinal biomarkers for Alzheimer disease (AD).[1,2]

Study details. Digital retinal photographs were collected from 144 individuals in the Australian Imaging, Biomarkers, and Lifestyle Study in Aging. Of these, 22 participants had previously been diagnosed with AD, and 122 did not have dementia.

The researchers used a computer-based technique to quantify CR—the central reflection observed in photographs of retinal vessels—and calculate the CR-to-vessel-width ratio (CRR).

Results. Significantly higher CRR levels were identified in patients with AD than in controls. However, this significance was reduced after the researchers adjusted for the apolipoprotein E (*APOE*) ε4 allele—one of the main genetic determinants of AD. Allele carriers also had a significantly higher CRR than did non-carriers, indicating that this gene influences AD risk through vascular effects.

Clinical implications. "We set out to update the way CR is measured, moving from a qualitative assessment typically employed by clinicians to a fully automated approach," said lead researcher Shaun Frost, PhD, a biomedical scientist at the Commonwealth Scientific and Industrial Research Organization in Perth, Western Australia.

"Using this new approach, we found further evidence that retinal changes might be utilized for early detection of AD and that the retina may also be useful as a novel model for noninvasive monitoring of the effects of *APOE ε4* on the central nervous system, particularly in cerebrovascular disease." *—Mike Mott*

1 Frost S et al. *Curr Alzheimer Res. 2017;13(11):1259-1266.*
2 Frost S et al. *J Alzheimers Dis.* 2010;22(1):1-16.

Relevant financial disclosures—Dr. Frost: None.

However, the report noted that uncertainty remains about the mechanisms and the dose threshold for radiation-induced cataractogenesis. In addition, more research is needed on dosimetry methodology and dose-sparing optimization techniques. It would take a huge research project to eliminate the uncertainty surrounding these issues, Dr. Dauer said. "Those studies would be exceedingly expensive, and it would take probably a million or more participants to tease out the impacts at these low-dose levels," he said.

Leaded glasses? The panel hopes that its report will prompt physicians whose workday exposes them to radiation to better protect their eyes, Dr. Dauer said. "Interventionalists already wear leaded aprons to protect their whole bodies from scattered x-rays. If they could put on a pair of leaded glasses [that don't restrict their eyesight], then they can reduce their dose to the lens by at least a factor of 10, if not more," Dr. Dauer said.

Strategic scans. The lenses in patients' eyes also can be protected if physicians adhere to the ALARA-dose principle ("as low as reasonably achievable") when planning imaging tests such as computed tomography (CT) scans of the head, he said.

"Are there ways to do that CT in which you reduce the dose to the lens of the eye while still getting a clear image of the patient? Is there a way to shield the eye? Is there a way to swing the gantry of the CT at a slightly different angle and reduce the lens dose significantly? Research to answer questions like these has already begun, and we likely will see more of that as a result of this report," he said.

The panel's summary recommendations were drawn from a 147-page report published last year.[2]

—Linda Roach

Average Radiation Doses

Procedure	Eye Dose (mSv), Unshielded/Shielded+
Hepatic chemoembolization	0.27-2.14/0.016-0.064
Iliac angioplasty	0.25-2.22/0.015-0.066
Neuroembolization (head, spine)	1.38-11.20/0.083-0.329
Pulmonary angiography	0.19-1.49/0.011-0.045
TIPS* creation	0.41-3.72/0.025-0.112

+ Range reflects variations in examination techniques and distance from isocenter.
* Transjugular intrahepatic portosystemic shunt
SOURCE: Vano E et al. *Radiation.* 2008;248(3):945-953.

1 Dauer LT et al. *Int J Radiat Biol.* Published online April 3, 2017.
2 Dauer LT et al. *Commentary No. 26—Guidance on Radiation Dose Limits for the Eye.* National Council for Radiation Protection and Measurements, www.ncrppublications.org/Commentaries. Accessed April 27, 2017.

Relevant financial disclosures—Dr. Dauer: None.

See the financial disclosure key, page 8. **For full disclosures,** including category descriptions, view this News in Review at aao.org/eyenet.