News in Review

COMMENTARY AND PERSPECTIVE

GENETICS

New Macular Dystrophy Discovered

RESEARCHERS FROM THE NEI HAVE identified a novel macular dystrophy that has yet to be named.[1] The finding came in an evaluation of individuals who had maculopathy without some of the hallmarks of classic Sorsby fundus dystrophy (SFD).

"We were able to identify a new mechanism for a maculopathy that has distinct characteristics," said Robert Hufnagel, MD, PhD, at the NEI. "Our findings suggest that the diagnostic odyssey of patients with macular dystrophy does not necessarily end with the first genetic test. A reconsideration of genetic variants in light of other findings and functional data is required to improve SFD diagnosis and management."

Background. SFD is an autosomal dominant form of macular dystrophy that typically presents in adults. Mutations in *TIMP3*, the gene that encodes tissue inhibition of metalloproteinases-3, have been implicated in SFD. Mutations in the C-terminal of TIMP3 cause accumulation of protein aggregates in the extracellular matrix between the retinal pigment epithelium (RPE) and vascular choriocapillaris. However, little is known about the role of mutations in the C-terminal of TIMP3 in SFD.

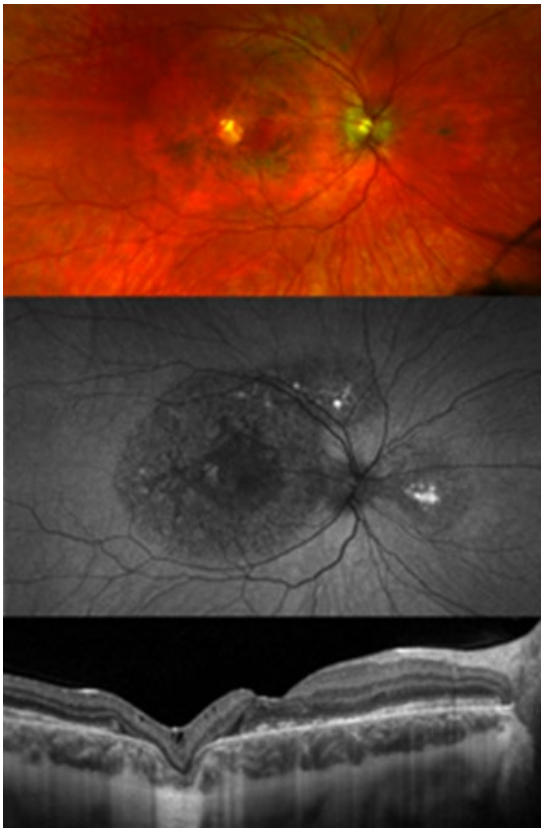
Study specifics. The NEI researchers set out to evaluate the pathogenic effects of mutations in the N-terminal of TIMP3 in two families who had diffuse maculopathy without choroidal neovascularization (CNV). They conducted clinical imaging, molecular genetic testing, and cosegregation analysis. They also performed biochemical analysis of TIMP3 variants to understand the pathogenic mechanisms of *TIMP3*-related macular dystrophy.

Findings. The researchers sequenced the DNA of 17 individuals and found that all 11 individuals with maculopathy harbored mutations in the N-terminal signal peptide variations (L10H or G12R) of TIMP3. These mutations were absent in the six individuals without macular dystrophy.

Distinct clinical characteristics. The 11 affected participants had clinical features atypical of SFD, including early onset, preserved useful central vision, paracentral scotomas due to paracentral atrophy, mottled hypoautofluorescence on fundus imaging, and outer retinal degeneration and RPE atrophy on OCT. None of the affected individuals had CNV or hemorrhage.

A new mechanism for retinopathy. "Considering that TIMP3 is a secreted protein and that signal peptides regulate protein trafficking and secretion, we hypothesized that the L10H and G12R variants would show altered protein secretion," Dr. Hufnagel said. Indeed, analysis of protein localization showed that although wild-type TIMP3 was abundant in the extracellular matrix, TIMP3-L10H and TIMP3-G12R peptide variants showed little to no extracellular deposition. In addition, while the SFD-associated S38C variant of TIMP3 showed impaired secretion and normal cleavage, the L10H and G12R variants exhibited defects in both cleavage and protein trafficking.

What's next? In commenting on the clinical relevance of these findings, Dr. Hufnagel said, "As we are developing gene therapies or mutation-agnostic therapies for retinal dystrophies, we must keep in mind that even when mutations are within the same protein,



NOVEL DYSTROPHY. *Retinal images of a patient with a* TIMP3 *mutation causing atypical symptoms. Despite extensive damage in the retina (dark circles), CNV is absent.*

Robert Hufnagel, MD, PhD, National Eye Institute

differences in pathogenic mechanisms could have different clinical outcomes and may require different treatment approaches."

He added, "We need to better understand the fundamental mechanisms of this new type of macular dystrophy and compare them to the mechanisms of other *TIMP3*-related retinopathies. We still need to understand the natural history of this condition so that we can identify the treatments and outcome measures that we should be considering."

—Christos Evangelou, PhD

1 Guan B et al. *JAMA Ophthalmol.* 2022;140(7):730-733.

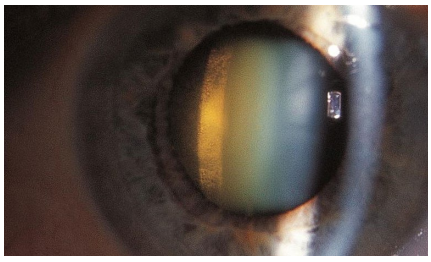
Relevant financial disclosures: Dr. Hufnagel—None.

CATARACT

Statins and Cataract Risk

DANISH RESEARCHERS HAVE FOUND that a genetic proxy that mimics statin treatment is associated with an increased risk of cataract development and the need for cataract surgery.[1]

The findings lend support to previous studies linking statins to lens opacities. But while none of those earlier studies conclusively demonstrated an association between statins and the risk of cataract development, this study is different, said Jonas Ghouse, MD, PhD, at Copenhagen University Hospital in Denmark. "Using genetics, we were able to show that proxies for lifelong statin treatment may increase the risk of lenticular opacities."



ASSOCIATION. *Both common and rare variants of the* HMGCR *gene were linked to cataract development.*

Study design. The researchers considered whether the presence of deleterious mutations in the *HMGCR* gene, which encodes HMG-CoA reductase,

PEDIATRIC OPHTHALMOLOGY

Brain Bleeds in Preemies Raise Risk of Long-Term Visual Impairment

SEVERE BRAIN BLEEDING IN PREMATURE INFANTS can lead to long-term vision problems, according to researchers at the University of Bristol in the United Kingdom.[1]

Study rationale. Intraventricular hemorrhage and ventricular dilation (IVHVD) is a common complication in premature infants. Severe IVHVD (grades 3 and 4) puts preterm infants at high risk for cognitive disabilities. An intervention known as DRIFT (drainage, irrigation, and fibrinolytic therapy) was developed as a method of "washing out" the ventricles. In a 2010 DRIFT study, the treatment was found to significantly improve cognitive outcomes.[2] A follow-up study of DRIFT, published in 2020, found the benefits of the intervention to be sustained over a 10-year period.[3]

Long-term follow-up. For this study, the U.K. researchers assessed the vision of the children in the DRIFT study. "The aim of our study was to examine a range of visual functions in a group of 10- and 11-year-old children who had experienced a severe complication of premature birth in the perinatal period," said lead author Cathy Williams, PhD. They also sought to discern whether there was any correlation between the children's vision and the severity of their IVHVD and explored the associations between visual outcomes, cognitive outcomes, and the need for extra help in school.

Study details. The researchers evaluated the visual exams of 32 children who were part of the DRIFT study. Investigators were masked as to whether each child had experienced grade 3 versus grade 4 IVHVD.

Results. All of the children had one or more visual impairments. The median number of impairments per child who experienced grade 3 and 4 IVHVD was three and six, respectively. Each additional visual impairment per child was associated with increased need for educational support at school, after adjusting for developmental age equivalence (odds ratio = 1.7, p = 0.015).

"We were surprised that all of the children had at least one vision problem, and several had multiple problems," Professor Williams said. Moreover, she said, the researchers also observed that "the more vision problems a child had, the more likely they were to be receiving extra help at school, even after adjusting for IQ."

Need for greater awareness. The study authors want clinicians to be aware of the high level of visual impairment present in children at least 10 years after severe IVHVD. They hope that developmental outcomes for such children might be improved if support for their visual impairments can be initiated as early as possible.

Professor Williams noted that neither parents nor pediatricians would be expected to know about these vision problems. "Babies who experience severe brain bleeds should have comprehensive vision checks as they grow. The child needs to be assessed by an eye care professional using appropriate and valid tests."

—Patricia Weiser, PharmD

1 Williams C et al. *Dev Med Child Neurol.* Published online June 23, 2022.
2 Whitelaw A et al. *Pediatrics*. 2010;125(4):e852-858.
3 Luyt K et al. *Arch Dis Child Fetal Neonatal Ed.* 2020;105(5):466-473.

Relevant financial disclosures: Professor Williams—NIHR: S.

are associated with the risk of cataract and/or cataract surgery. (HMG-CoA reductase is a crucial enzyme in the cholesterol pathway and thus is the target of statins.)

To test their hypothesis, they analyzed UK Biobank genetic sequencing data of more than 402,000 unrelated European individuals between 40 and 69 years of age. The Biobank data allowed them to create a genetic score weighted by each variant's ability to lower low-density lipoprotein (LDL) cholesterol. Variants with larger effects were given larger weights.

Link emerges. The researchers found a strong association between the *HMGCR* score and LDL levels. Specifically, a 38.7 mg/dL reduction in LDL score was associated with higher risk for both cataract (odds ratio [OR], 1.14) and cataract surgery (OR, 1.25).

To investigate whether the reported association was specific to the HMG-CoA pathway, the researchers looked at cataract risk associations between other genetic variants with known cholesterol-lowering effects. In particular, they considered genetically proxied inhibition of *PCSK9* and *NPC1L1* on circulating LDL levels and cataract. They found no association.

"What was important to investigate was whether it was the inhibition of the gene, rather than a global lowering of the cholesterol, that caused the reported association," Dr. Ghouse said. "These results indicated that it was the inhibition of *HMGCR*, and not general LDL-lowering, that was associated with cataract risk."

Clinical implications. Dr. Ghouse stressed that the reported gene association mimics long-term statin treatment, as occurs in patients with familial hypercholesterolemia. Thus, they may not translate to the initiation of statins later in life. For now, the findings should not deter treatment, but they should be disclosed to patients, he recommended. —*Miriam Karmel*

1 Ghouse J et al. *J Am Heart Assoc.* 2022;11(12):3025361.

Relevant financial disclosures: Dr. Ghouse—None.

RETINA

Gas Versus BSS After Diabetic Vitrectomy

IN A STUDY OF PATIENTS UNDER-going diabetic pars plana vitrectomy (PPV), vitreous substitution with sulfur hexafluoride (SF_6) gas tamponade proved superior to balanced saline solution (BSS) in reducing the occurrence of postoperative vitreous hemorrhage (VH).[1]

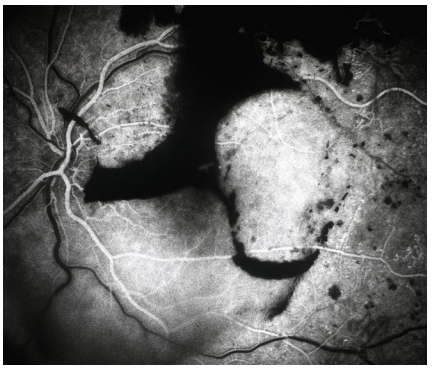
While the literature has been inconclusive regarding the merits of SF_6 gas versus BSS, the results of this study were robust enough to suggest SF_6 gas tamponade may be used during PPV as a means of reducing postoperative VH in patients with proliferative diabetic retinopathy (PDR), said Ryan B. Rush, MD, at Panhandle Eye Group in Amarillo, Texas.

How the study was conducted. The study, conducted at a university-associated teaching hospital in Montemorelos, Mexico, included 96 PDR patients who needed PPV for nonclearing vitreous hemorrhage. Patients were prospectively randomized to receive either 20% to 30% SF_6 gas tamponade or BSS (the control).

All patients received a baseline ophthalmic evaluation within 28 days before undergoing PPV, followed by post-op examinations at 15, 40, and 185 days after the procedure. The primary outcome was the incidence of postoperative VH during six months of follow-up; secondary outcomes included BCVA and unplanned PPV.

What the results showed. At six months, the incidence of postoperative VH was 11.1% (6/54) in those who received gas tamponade, versus 33.3% (14/42) in those who received BSS. The incidence of unplanned PPV during the trial period for postoperative VH was 3.7% in the SF_6 gas group and 14.2% in the BSS group.

Mean BCVA did not significantly differ between the groups at the six-month mark, with both cohorts improving from baseline. The SF_6 gas group improved from 20/796 to 20/94, while the BSS group improved from 20/778 to 20/112.



HEMORRHAGE. *This eye with PDR has a moderate vitreous hemorrhage. The VH is blocking the fluorescence in this early-phase photograph.*

What about complications? In this study, the concentration of SF_6 gas was either nonexpansive or slightly expansive, so IOP elevation was similar in both groups. In addition, the incidence of retinal breaks and detachment was low for both groups.

As all phakic subjects underwent cataract surgery at the same time as PPV, the researchers were unable to draw a conclusion regarding cataract development. (The researchers made a compassionate decision to combine surgeries because subjects were indigent, with potentially limited access to cataract surgery.)

The only observed intraoperative difference was longer surgery time in the gas tamponade group, by approximately 9 minutes. The time might be reduced outside the research setting, as the gas mixture can be drawn while other surgical maneuvers are still being performed, the researchers noted.

Bottom line. While the conclusions may not be valid for other underlying diabetic pathology, Dr. Rush said that for cases of diabetic VH without traction, "I believe the results provide some guidance." —*Miriam Karmel*

1 Rush RB et al. *Am J Ophthalmol.* 2022;242:173-180.

Relevant financial disclosures: Dr. Rush—None.

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