Study uses new tools, machine learning to investigate major cause of blindness in older adults

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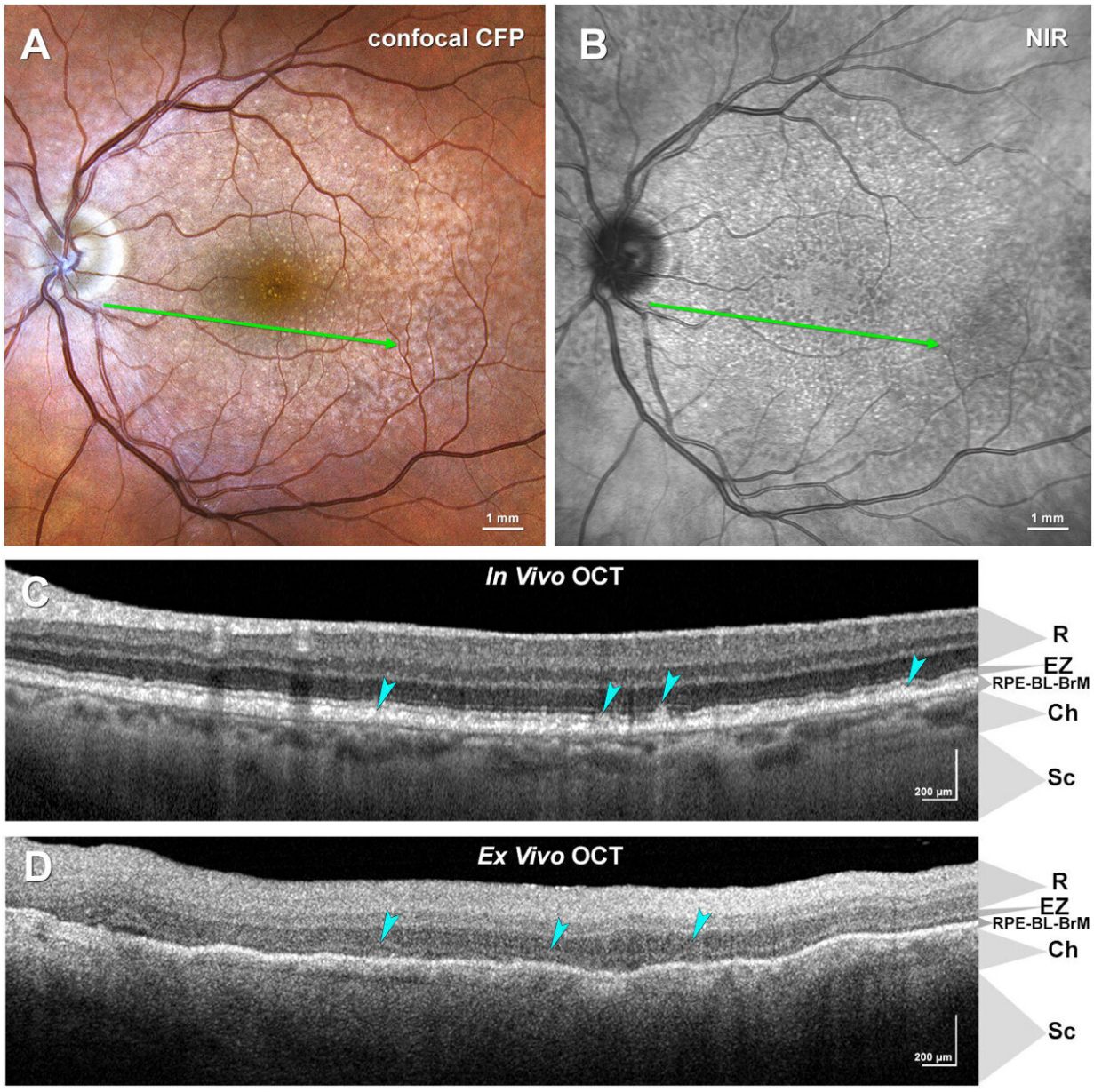

Multimodal imaging of subretinal drusenoid deposits (SDD) in age-related macular degeneration (AMD). Credit: *Frontiers in Ophthalmology* (2023). DOI: 10.3389/fopht.2023.1258734

Age-related macular degeneration is a common disease of aging and a leading cause of blindness in older adults, although blindness can be prevented if AMD is treated early. Advanced AMD is treatable only in about 15% of cases by injecting medications directly into the eye, which is burdensome and expensive for patients and their families.

Developing prevention or early detection tools could greatly improve the chances of avoiding advanced disease and would help AMD patients maintain quality of life for longer.

Vanderbilt researchers, in collaboration with investigators from the University of Alabama at Birmingham, the Delft University of Technology, University Hospital Bonn, and Molecular Horizon have developed new protocols to study which molecular pathways might be important in the aging retina and what might cause the formation of deposits in the eye that confer high risk for AMD.

The paper, "Lysolipids are prominent in subretinal drusenoid deposits, a high-risk phenotype in age-related macular degeneration," was published in the journal *Frontiers in Ophthalmology*.

"A deposit called drusen, found in the eyes of patients with AMD, has been studied for 150 years," said Kevin Schey, lead investigator on the paper.

"On the other hand, subretinal drusenoid deposits or SDD—also known as reticular pseudodrusen—were first shown by pathology studies in the 1980s. The frequency of these deposits and their strong relationship to advanced disease were not appreciated until the last 15 years."

The presence of SDD in eyes, although indicative of an early stage of AMD development, may affect the outcomes of treatments if not properly diagnosed.

To better understand SDD, Schey, professor of biochemistry and deputy director of the Mass Spectrometry Research Center, and colleagues used imaging mass spectrometry coupled with automated machine learning to analyze their molecular components.

In addition, the investigators developed a nano-high-performance liquid chromatography tandem mass spectrometry method to provide high-sensitivity analysis of the lipids in very small samples such as SDD in thin retina sections.

The study provides the first and most comprehensive data to date about the composition of SDD and resulted in the identification of a salient component: lysolipids, specialized molecules important for the synthesis and breakdown of cell membranes of retinal cells such as photoreceptors (the cells that initiate vision).

Additional studies using classic microscopy techniques showed morphological details of the smallest and earliest lesions and identified an enzyme important in the formation of the lysolipids.

The abundance of lysolipids in SDD implicates lipid remodeling or degradation in the formation of the deposits. Yet, in addition to providing clues about SDD formation and function, the development of these protocols will allow the investigators—and others around the

world—to probe SDD and other retinal lesions and potentially identify additional molecular pathways critical to the development of AMD.

Inter-institutional collaboration was very important for this study. The University of Alabama at Birmingham provided histologic evaluation and access to freshly preserved human eye tissue to ensure the most accurate microscopic and molecular analyses.

The MSRC, which recently established the first Mass Spectrometry Core Center of Excellence with Bruker Daltonics, provided the cutting-edge equipment and expertise needed for all aspects of sample processing and imaging mass spectrometry.

The Delft University of Technology developed and implemented automated machine learning strategies to help analyze the enormous amount of generated mass spectrometry data. The University Hospital Bonn and Molecular Horizons provided additional tissue samples and data analysis tools, respectively.

"This study would not have been possible without all the collaborators coming together," Schey said. "Each team, particularly the labs of Christine Curcio at UAB and Raf Van de Plas at Delft, brought complementary skills and tools that allowed us to successfully bring this study from conception to fruition."

From here, Schey and his team of Vanderbilt researchers will continue to dig into the mass spectrometry data and plan on testing hypotheses generated from this study's results. "We will also continue to improve our methods of analytical chemistry to expand the available information about the early stages of AMD for the scientific community," Schey said.

"We hope that, in addition to our ongoing studies, other researchers will

test the biological mechanisms involved with deposit formation and find new ways to prevent or treat them."

All of which looks promising—pun intended—for older adults who hope to minimize the risk of falls and the loss of personal independence that accompanies loss of vision.

More information: David M. G. Anderson et al, Lysolipids are prominent in subretinal drusenoid deposits, a high-risk phenotype in age-related macular degeneration, *Frontiers in Ophthalmology* (2023). DOI: 10.3389/fopht.2023.1258734

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