

CLINICAL UPDATE

Personalized Genetic Testing Evaluated

While important insights into disease biology and potential therapeutic strategies are coming from the discovery of new genetic risk factors — including genes associated with age-related macular degeneration (AMD) — the ability to reliably gauge individual risk for specific diseases such as AMD is a long way off, reports Michael B. Gorin, M.D., Ph.D., the Harold and Pauline Price Professor of Ophthalmology at UCLA's Jules Stein Eye Institute.

In a study published in the online journal *PLoS Genetics*, Dr. Gorin and colleagues at the University of Pittsburgh Graduate School of Public Health note that although many companies offer personalized genetic testing for diseases such as cancer, heart disease, and diabetes — and several offer macular degeneration testing — even strong associations between gene variants and disease do not necessarily translate into useful clinical tools for

evaluating individual risk. “Our study should be interpreted as a voice of caution,” Dr. Gorin says. “It’s a mistake to assume that for these complex diseases, we’re going to be able to go right from genetic studies to having clinically useful tests.”

SNP Genotyping for AMD. The study focused on single nucleotide polymorphisms, or SNPs: Variations in short DNA sequences that have been linked to the presence of particular diseases, and that exist in the millions in the human genome. A number of companies currently offer individualized estimates for disease risk based on genome-wide SNP genotyping. These tests typically scan 500,000 to 1 million SNPs, searching for only a handful associated with a specific disease.

Dr. Gorin’s group focused on diseases for which there are strongly associated genetic variants — including AMD, type 2 diabetes, prostate cancer,



cardiovascular disease and Crohn’s disease. The researchers found that a strong genetic association did not guarantee they could accurately discriminate between actual disease

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Adult Strabismus Often Caused by Ligament Wear and Tear, Not Neurological Problems

It has long been believed that most cases of new adult strabismus are caused by neurological problems. But a Jules Stein Eye Institute research team has presented evidence from high-resolution MRI studies of the eye sockets that many adult cases of strabismus instead result from wear and tear on the ligaments that support the eye muscles.

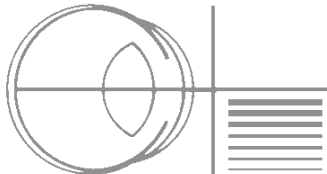
“As these ligaments give out and begin to sag or break, eye movements are compromised in a way that causes strabismus and patient complaints of double vision,” explains Joseph L. Demer, M.D., Ph.D., Leonard Apt Professor of Pediatric Ophthalmology, whose findings were published in the *Journal of the American Association of Pediatric Ophthalmology and Strabismus*.

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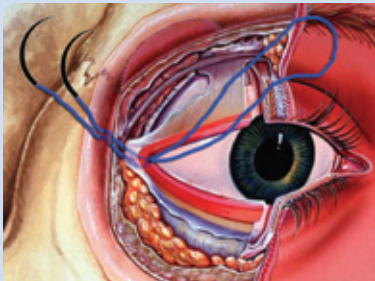
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JULES STEIN EYE INSTITUTE

Minimal-Incision Closed Canthoplasty Results in Faster Healing and a Better Cosmetic Result



Using a double-armed Maxon suture, the needles pass through the grey line at the lateral conjunctiva, and then through the periostium inside the lateral orbital rim.



After lysing the lateral canthal tendon adjacent to its bony insertion, the lower eyelid lateral fat pad is accessed through the small lateral upper eyelid incision.



The double armed suture is in place, ready to attach the cut end of the tarsus to the lateral orbital periostium.

A Minimally Invasive Approach to Lateral Canthoplasty

Ophthalmic plastic surgery is moving toward increasingly smaller incisions and less invasive surgical approaches. Among the best illustrations of this trend is the approach that has been pioneered in the last several years at UCLA's Jules Stein Eye Institute to one of the most common canthoplasty procedures.

Lateral canthoplasty is a core procedure used to correct horizontal laxity, either alone or as part of more complex surgeries. The surgery has traditionally required a horizontal incision between the upper and lower eyelids to separate the canthal tendons. This carries a small degree of risk for a cosmetic or functional disturbance at the delicate angle where the upper and lower eyelids meet: The incision can destabilize the upper and lower eyelids and cause a scar or web.

Less Invasive Technique. JSEI ophthalmic plastic surgeons have designed a technique that accomplishes the same surgical goal as the traditional procedure, but without requiring an opening in the wet tissue between the upper and lower eyelids. Instead, Robert A. Goldberg, M.D., professor of ophthalmology and chief of JSEI's Orbital and Ophthalmic Plastic Surgery Division, uses a small lateral upper-eyelid incision to access and disinsert the lateral canthal tendon. A double-armed suture is then passed through the grey line

externally and used to reattach the tendon to the orbital rim periosteum. The result is a shorter surgery, with less pain and a faster recovery for the patient. The small incision can also be utilized for additional surgical steps as required.

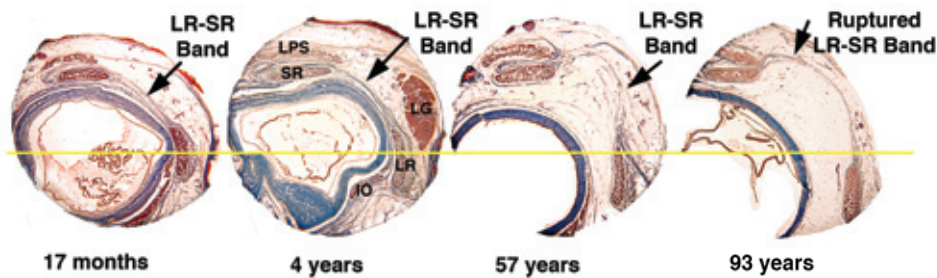
Dr. Goldberg says no complications related to the procedure have occurred in the hundreds of closed canthoplasty cases he has done since adopting the new approach approximately five years ago. The less invasive approach can be used for the overwhelming majority of lateral canthoplasties; cases in which there is severe laxity may still require the open procedure. Dr. Goldberg, along with Ronald Mancini, M.D., and Mehryar Taban, M.D., have taught it to colleagues both at meetings and at UCLA, where many have come to observe. They are currently preparing a paper on the approach and the outcomes to date.

"The results of minimal-incision closed canthoplasty have been comparable to the traditional open canthoplasty procedure, and because the delicate lateral mucocutaneous junction is not incised, healing is faster and incision complications are significantly reduced," Dr. Goldberg says. "We see less redness and less discomfort, and patients return to work sooner. "They get a better cosmetic result, and psychologically they feel less violated." 🌐



The small incision canthoplasty was used here to address postoperative canthal dystopia; improvement in the canthal height is noted postoperatively, with the short scar hidden in the upper eyelid fold.





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“In these cases the strabismus is not due to a neurological problem such as a stroke, a brain tumor, or nerve damage.”

Dr. Demer’s study has major implications for the diagnosis and treatment of strabismus in adults. “I have seen patients who have had extraordinarily intensive and costly neurological evaluations,” he says. “If this connective tissue problem had been recognized early on, there would have been no need for these diagnostic tests and all of the anguish that goes with them.”

Sagging of Tissues. Dr. Demer suspects that the majority of adult patients who present with certain categories of strabismus have the disorder as a result of sagging of the tissues around the eye. This is particularly the case among older patients. An ophthalmologist can identify typical clinical signs by looking at the patient’s face — including drooping of the eyelid and characteristic changes in the appearance of the upper eyelid and its relationship to the eye socket. These signs should be followed up with an imaging study of the orbit to identify specific diagnostic changes. If the diagnosis of strabismus on the basis of tissue damage is confirmed by imaging, the appropriate strabismus surgery may be entirely different than if a neurological cause were identified.

“Heavy eye syndrome” was coined based on the long-held belief that extremely nearsighted eyes are larger than normal and thus heavier, causing them to sink in the eye socket, resulting in strabismus. Researchers, including Dr. Demer’s group, discovered that it was not eyeball heaviness but a marked sag of one or more muscles that caused the eye-crossing. The current paper by Tina Rutar, M.D., and Dr. Demer indicates

that heavy eye syndrome isn’t unique to highly nearsighted people; it commonly occurs to a milder degree in non-nearsighted patients as a simple consequence of aging.

Evidence for Non-Neurological Cause.

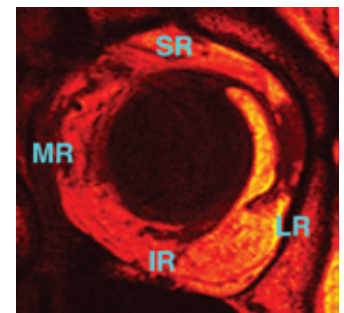
The paper is the most recent strabismus-related discovery to be reported by Dr. Demer’s group, which has received grant support from the National Eye Institute for the last 20 years to study the mechanical basis of the disorder. The evidence Dr. Demer and colleagues present for the more benign, non-neurological cause of strabismus in adults is compelling. In addition to using high-resolution MRI to see the eye muscle paths and ligaments directly, they conducted microscopic examinations of anatomical donations from cadavers at various ages to learn more about how the ligaments change over the life span. Studies in normal people at various ages showed that the ligaments thin and the muscles sag with age. Finally, surgical exploration of patients who presented with strabismus apparently caused by tissue wear and tear confirmed that the ligaments were degenerated. By repairing the consequences of the degeneration — for example, by operating on sagging horizontal-acting muscles to correct vertical strabismus — Dr. Demer’s team has been able to straighten the eyes.

“Strabismus in adult patients, particularly the elderly, is often not due to neurological problems, but rather connective tissue wear and tear,” Dr. Demer concludes. “Ophthalmologists should look for sag around the eyelids, ask about previous eyelid surgery, and pay careful attention on orbital CT or MRI scanning to the positions of the lateral rectus muscles in both eyes.”

◀ Coronal histological sections from the left eyes of humans aged 17 months to 93 years show progressive thinning and ultimate rupture of the LR-SR band ligament, allowing the lateral rectus (LR) muscle to sag inferiorly. LR sag tends to cause esotropia and limited upward gaze. Masson’s trichrome stain stains collagen of sclera and connective tissues blue, and muscles and glands red.

IO - inferior oblique muscle
 LG - lacrimal gland
 LPS - levator palpebrae superioris muscle
 SR - superior rectus muscle

“Heavy eye syndrome” was coined based on the long-held belief that extremely nearsighted eyes are larger than normal and thus heavier, causing them to sink in the eye socket, resulting in strabismus.



▲ Coronal MRI scan of left orbit of 87-year-old woman with acute left hypotropia, showing inferior displacement of LR muscle due to rupture of the LR-SR band ligament.

MR - medial rectus muscle
 IR - inferior rectus muscle



AARP *The Magazine* ranks Jules Stein Eye Institute as No. 3 in the country for complex eye-care referrals.



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Genetic Testing — continued from cover

cases and controls. The vast majority of patients (84% to 88%) classified as being at high risk for AMD based on SNPs in three “risk genes” would not go on to develop the disease, according to the calculations. Even in a population in which the prevalence of AMD is as high as 15% — those 80 and older — testing based on the three genes had a positive predictive value of only 30%. Part of the problem may be a statistical one. To provide meaningful insights, a test for disease risk needs to accurately identify positive cases and, at the same time, provide a low false-positive rate. A challenge with current approaches to genetic testing is that they are based on a small number of common variants, making it likely that people will be identified as being at high risk who may not be at risk at all.

The Argument Against Testing. The argument against individual genetic testing for AMD and other complex diseases is not solely scientific,

Dr. Gorin explains. There is also the potential psychological stress for people who learn they are more susceptible to a disease — often without understanding the context of the risk — as well as the potential for a false sense of security for people who test negative for a genetic variant, but may still be at risk. Moreover, most physicians lack the genetic training to make sense of risk calculations and advise accordingly. Whether genetic testing for complex diseases will ever become clinically useful in and of itself remains unclear. On the other hand, in the future it might be possible to combine genetic profiling with behavioral and environmental risk factors to come up with a predictive model for a disease such as AMD.

As for the current applications of genetic studies, Dr. Gorin says: “People should view the genetic research with excitement and enthusiasm because of what we may learn, but we shouldn’t be confused about how to use the data appropriately.”



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