NewYork-Presbyterian

ADVANCES IN OPHTHALMOLOGY

Affiliated with Columbia University College of Physicians and Surgeons and Weill Cornell Medicine

FALL/WINTER 2015

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A New Look at Modern Cataract Surgery

Cataract removal traditionally has been one of the most common refractive surgical procedures in the United States with some three to four million performed each year. Major advancements in surgical technique and technologies have led to a dramatic increase in volume with projections that it will only continue to increase in the future. According to the National Eye Institute, by 2050 the number of people with a cataract is expected to double from 24.4 million to about 50 million.

Such an increase and corresponding treatment burden bears consideration today, says **Christopher E. Starr, MD**, ophthalmologist, Department of Ophthalmology, NewYork-Presbyterian/Weill Cornell Medical Center. "In some cases there are even predictions for possible shortages of ophthalmologists," says Dr. Starr, who, in addition to having an active clinical practice, is Director of Ophthalmic Education, Director of Refractive

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Dr. Christopher E. Starr

Uncovering the Basic Origins of Ocular Diseases

A rare eye disorder marked by color blindness, light sensitivity, and other vision problems can result from a newly discovered gene mutation identified by an international research team that includes **Stephen H. Tsang, MD, PhD**, the Laszlo Z. Bito Associate Professor of Ophthalmology, Pathology, and Cell Biology, Department of Ophthalmology at Columbia University Medical Center.

> "I think the important lesson of this study is that it demonstrates how advanced technologies are bringing precision medicine to the field of ophthalmology. Certain diseases may look the same based on the clinical diagnosis, but we're finding that each patient is a little bit different and may benefit from a personalized approach to treatment."
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> — Dr. Stephen H. Tsang

The researchers, whose findings were published in the July 2015 issue of *Nature Genetics*, determined that mutations to a gene called ATF6, a key regulator of the unfolded protein response, can lead to achromatopsia, an autosomal recessive disorder characterized by color blindness, photophobia, nystagmus, and severely reduced visual acuity. The unfolded protein response is a mechanism cells use to prevent the dangerous accumulation of unfolded or misfolded proteins.

Mutations in ATF6 have been implicated in diabetes, Alzheimer's, and other disease models, but this is the first time that they have been directly linked to human disease. Achromatopsia is a disorder of the retina's cone cells; rod cells are unaffected. There is currently no effective treatment for the disease, which appears in infancy and typically does not progress.

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Surgery, and Co-Director of the Fellowship Program in Cornea, Cataract and Laser Vision Correction Surgery at Weill Cornell Medicine. "Right now, cataract surgery is widely available and there are enough ophthalmologists to perform it. However, with the baby boomer generation, millions of new people over the age of 65 – as their cataracts become visually significant – will place a greater demand for more doctors to accommodate them."

Faster, Safer, with Fewer Risks

During the past several decades, cataract surgery has undergone rapid development and improvements. "In the field of ophthalmology, almost every six months there is a major development – a new pharmacologic drop, an injectable for macular degeneration, a new technique or technology," says Dr. Starr, an accomplished researcher and lecturer who has contributed extensively to the ophthalmic literature and has served as principal investigator of numerous clinical trials.

> **"My criteria for doing cataract surgery is when the cataract is impeding daily activities in some way. The latest and greatest technology is one thing, but you still have to have that meaningful, personalized relationship with the patient to figure out what's going to work for their unique situation."**
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> **— Dr. Christopher E. Starr**

Cataract surgery today is being offered to patients earlier because the surgery has become quicker and safer as compared to 30 years ago when the risks were much higher for infection, retinal detachment, or other problems. "Now, those risks are much lower, so we are not waiting for cataracts to be 'ripe' as they used to say," says Dr. Starr. "Back then you would wait until the patient was nearly blind to perform the surgery, because at that point the benefit outweighed the potential risks and the risks were substantial."

The criteria today for cataract removal are based on a number of factors. "A common criteria is when a patient is having a hard time functioning and daily activities have been inhibited in some way," says Dr. Starr, who notes that people are now choosing to have surgery sooner and earlier, a testament to the evolution of surgical techniques, technologies, and antibiotics. "Everything has improved over the years, from the pre- to intra- and postoperative care."

The various types of cataracts have visual significance: blurring, clouding, glare, halos, poor vision, declining night vision, sensitivity to light, all of which are classic symptoms. "However, a patient with 20/80 vision, which by most standards is not great vision, can say, 'I can function and do everything that I need to do just fine,'" says Dr. Starr. "The patient may have a mild to moderate cataract, but if they say they're doing fine, it's OK to monitor it closely. Conversely, I've had patients with 20/25 vision, which is relatively good vision, say, 'I'm going crazy with this cataract, I can't do this or that, I don't feel safe driving, I can't do my job.' Those people are bothered enough with the early cataract that we proceed with surgery. So there is a spectrum; it really involves a conversation between doctor and patient as to when the timing is right."

Dr. Starr emphasizes that each patient is different, as are his or her needs. "Most commonly, what people want is their distance vision corrected for driving, walking down the street, watching TV, getting up in the middle of the night, and navigating the hallways," he says. "If they had to pick a pair of near or far glasses to wear on a day-to-day basis, they would pick reading glasses. But, again, in the modern era, with our new advances in lenses, we now have lenses that can provide distance vision, intermediate vision, and near vision all in the same eye." This is accomplished with multifocal or accommodating lenses, which are generally not covered by insurance.

Improving on Standard Techniques and Technologies

The standard of care in cataract surgery is still phacoemulsification in which the eye's internal lens is emulsified with an ultrasonic handpiece and aspirated from the eye. Aspirated fluids are replaced with irrigation of balanced salt solution, thus maintaining the anterior chamber, as well as cooling the handpiece. "Cataract surgery is largely still manual," says Dr. Starr. "The high speed, ultrasound handpiece enters the eye through very small incisions. Those incisions have gotten smaller with time, and the machine has been refined with the tips getting smaller and the intraocular lenses {IOLs} getting better."

Dr. Starr has developed a modification of the phacoemulsification technique by prolapsing the cataract out of the capsule and pre-chopping it into pieces with manual instruments rather than using the actual ultrasound device. This is called the pop and prechop technique. "I have found that this reduces the amount of phacoemulsification energy one needs, and by lowering the energy, it is a bit safer with less potential for collateral trauma," he says. "You can remove the cataract in a safer location inside the eye – at the iris plane – as opposed to deeper in the eye, which is closer to the posterior capsule. You want to preserve that posterior capsule during surgery because that is where the new lens sits. We've studied this technique in over 300 eyes and found it works really well and improves the safety. The technique has also been used by trainee surgeons with great results."

Dr. Starr recalls the early days of cataract surgery in which large corneal incisions were needed, requiring multiple stitches to close the wound. "Today, the surgery is largely sutureless, down to a sub-2.0 mm incision and 99.9 percent of the time no stitches are required," he says. "This has led to faster healing and safer surgery, but, nonetheless, I make a point to fully inform my patients that there are still real risks."

Among the rare but possible complications are endophthalmitis, which in some cases can lead to permanent, irreversible blindness; TASS, or toxic anterior segment syndrome, which is a robust, inflammatory process; and hemorrhagic choroidal detachment, an expulsive hemorrhage. Patients who are on anticoagulants or older patients with hypertension are at risk for this condition. There are also more mild complications following surgery that include corneal swelling, macular swelling, and retinal tear or detachment.

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Uncovering the Basic Origins of Ocular Diseases

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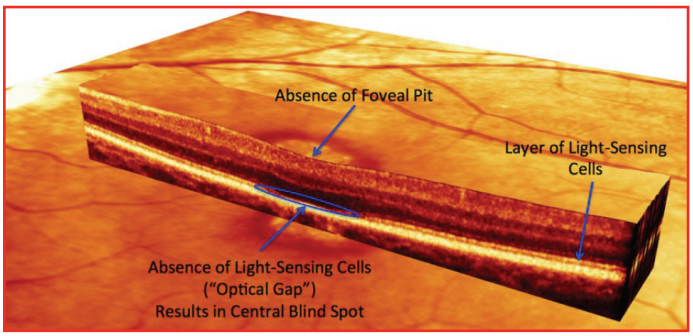
The new mutations were initially identified by sequencing the exomes of three children with achromatopsia who receive their care at NewYork-Presbyterian. None of the children had mutations in the five known achromatopsia genes. ATF6 mutations were subsequently observed in 15 achromatopsia patients from nine other families in the study. All of the patients were found to have significant fovea hypoplasia, a characteristic not commonly seen in other achromatopsia patients.

By analyzing skin cells from achromatopsia patients and their unaffected family members, the researchers confirmed that the ATF6 mutations were interfering with the signaling pathway that regulates the unfolded protein response. Surprisingly, the patients had no other ATF6-related abnormalities. "ATF6 is found in every cell of the body, but for some reason only the cone cells were affected," says Dr. Tsang, an internationally recognized clinician and geneticist specializing in the treatment of retinal disorders.

The researchers estimate that ATF6 mutations account for only about one percent of cases of the disease. "As we sequence more and more achromatopsia patients, we're likely to identify other genes," says Dr. Tsang, "I think the important lesson of this study



Cross Section of Diseased Retina: Optical Coherence Tomography (OCT) imaging reveals the loss of outer segments in foveal cone cells in the "optical gap" of a patient with ATF6A defects. (Courtesy of the Laboratory of Dr. Stephen Tsang)

is that it demonstrates how advanced technologies are bringing precision medicine to the field of ophthalmology. Certain diseases may look the same based on the clinical diagnosis, but we're finding that each patient is a little bit different and may benefit from a personalized approach to treatment."

"This finding is an example of the finest clinically based science that will ultimately allow us to overcome preventable vision loss," says **George A. (Jack) Cioffi, MD**, Chair of Ophthalmology and Ophthalmologist-in-Chief at NewYork-Presbyterian/Columbia.

Dr. Tsang has produced an impressive body of work that spans fundamental basic science to the biochemical and genetic basis of retinitis pigmentosa (RP) to preclinical trials for gene therapy to treat the disease. He has published on biochemistry and physiology of phosphodiesterase, and was the first to generate a genetically modified mouse model for RP, which he then used to develop gene therapy approaches that successfully repaired the photoreceptors. This approach is now ready for trials in RP patients.

In another recent investigation, Dr. Tsang and his research colleagues have begun exploring new pathways into disease etiology, drug development, and cell therapeutics by using induced pluripotent stem cells (iPS cells) created from patient

Dr. Stephen H. Tsang

cells. In his laboratory, Dr. Tsang generated iPS cells from two patients with retinitis pigmentosa. By taking these iPS cells and delivering a copy of them via gene therapy, Dr. Tsang was able to reverse the defects that this particular gene mutation causes, helping to advance the development of genomic science.

RP has multiple genetic sources, including a gene of unknown function called membrane frizzled-related protein (MFRP). Dr. Tsang's study demonstrated that MFRP mutations lead to defects in actin organization, apical microvilli, and "leaky" cell-cell junctions – effects that could be reversed, both in patient cells and in mice, by delivering a wild-type copy of the gene via gene therapy vectors. In effect, says Dr. Tsang, the study provided his team a budget-conscious way to test its vectors. "It's more cost-efficient to do testing of your viral vectors in culture than doing it *in vivo*," he explains.

Dr. Tsang has also collaborated with researchers around the country in studies of CAPN5 mutations that have been linked to autosomal dominant neovascular inflammatory vitreoretinopathy.

"Dr. Tsang's innovative research continues to unfold the genetic basis for a variety of ocular diseases," says Dr. Cioffi.

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More recently, femtosecond laser technology, which has been used in LASIK surgery, is also advancing cataract surgery to replace or assist the use of the handheld surgical tool for the corneal incision, anterior capsulotomy, and lens and cataract fragmentation. Use of a laser can improve the precision, accuracy, and reproducibility of each of these steps, potentially reducing risks and improving visual outcomes.

An Eye to the Future

"This technology is going to be the beginning of many advances," says Dr. Starr. "The femtosecond laser can make some of the initial entrance incisions, as well as relaxing incisions for reducing astigmatism, very precisely and without the human hand being involved. The laser can pre-fragment the lens as well, but, again, even with these advances in technology, we still need to emulsify and remove the cataract, as well as place the IOL with the human hand. There is no truly automated cataract surgery yet. Will we have that someday? Perhaps, but no time soon. Will we have drops to remove cataracts or prevent cataracts at some point? We might. However, today, overwhelmingly the outcomes with cataract surgeries are impressively good and most people ultimately do very well."

Dr. Starr anticipates continued enhancement of IOLs in the future. "Traditionally the monofocal lenses can correct a single distance of vision, typically far, but the patient still has to wear glasses for the other, typically near," he says. "We have newer advanced technology lenses, which can provide a full range of vision and leave patients spectacle-free after surgery. As good as these currently available lenses are, there is always room for improvement; and that is what the near future will hold. We'll have better lenses that can restore a combination of focusing – true presbyopia reversal, restoring focusing, but without sacrificing distance or increasing issues such as glare, decreasing night vision, or reducing optical quality. I liken it to television with high definition. That's what we want to be able to provide our patients – super, beyond high-definition eyeglass-free vision."

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