DISCOVERY
THE DISCOVERY EYE FOUNDATION

The Discovery Eye Foundation supports research, education and advocacy related to sight-threatening eye diseases and their treatments, improving the quality of life for patients and their families.

Thanksgiving 2015

What Letter is Your Haplogroup?

Research on mitochondrial DNA shows promise for treating AMD

For the past few years, DEF Research Director Dr. M. Cristina Kenney has been researching the relationship of mitochondria and age-related macular degeneration (AMD). She found that damaged mitochondria from people with AMD send signals that can cause retinal cells to die at an increased rate, compared with people who had healthy mitochondria and no AMD. That research led to the exploration of stimulating mitochondria to support retinal cell health in an effort to retain or restore vision for people with AMD.

The incidence of AMD varies among different ethnic/racial populations.

Mitochondria in Cells

Cells are the basic building blocks of all living things. The human body is composed of trillions of cells. They provide structure for the body, take in nutrients from food, convert those nutrients into energy and carry out specialized functions. Cells also contain the body's hereditary material (DNA), so they can make copies of themselves.

Mitochondria are tiny structures inside cells whose function is to produce energy, like batteries in a flashlight, to keep cells alive. Each cell contains hundreds to thousands of mitochondria, which are located in the fluid that surrounds the nucleus. Although most DNA is packaged in chromosomes within the nucleus of a cell (nuclear DNA), mitochondria also have a small amount of their own DNA, known as mitochondrial DNA (mtDNA). Because only egg cells contribute mitochondria to a developing embryo, only females can pass on mtDNA to their children.

Mitochondrial Haplogroups

The mtDNA can be classified into categories called "haplogroups," which represent different ancient, geographically separated groups. For example, African-Americans and people of ancient African lineage have inherited L haplogroup mitochondria from their mothers — no matter where they currently live.

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The Cybrid Model

Creating cybrids to study age-related diseases

DEF Research Director Dr. Cristina Kenney's research has shown that mitochondrial DNA (mtDNA) from different ethnic/racial populations may play a key role in determining that population's resistance or susceptibility to disease (see "What Letter is Your Haplogroup?" on the front page). In order to study these effects, Kenney developed the "cybrid" model. Cybrids are cell lines with identical nuclei but the mtDNA from individuals of different ethnic/racial groups. The comparison of an individual's mitochondria with that from other ethnic/racial groups (African, European, Asian or Ashkenazi Jewish) allows us to determine if their mitochondria define that population's susceptibility or resistance to disease and response to drugs.

Kenney's cybrids are made with mitochondria from the blood taken from living donors. Looked at individually, they are all really "personalized cybrids," because each cybrid test system has the mitochondria from the original donor and reflects the responses of that donor.

Kenney is partnering with Dr. Pinchas Cohen, dean of the University of Southern California, Leonard Davis School of Gerontology, to explore how novel, small proteins from mitochondria might be used to treat various age-related diseases. Cohen's laboratory has discovered and characterized many of these new proteins, called "mitochondrial derived peptides" (MDPs). His work has shown that these MDPs can protect brain cells from damage and early death, such as what occurs in Alzheimer's disease. Cohen and Kenney are now testing these MDPs in the K and H cybrids to assess their protective effects to stop retinal cell death, such as what is seen in AMD.

"Our cybrid system represents a very powerful technique. We are now using the Ashkenazi Jewish population to learn how the mitochondria, with their unique mtDNA, influence risk factors for AMD. We plan to extend the study to investigate Ashkenazi Jewish people's susceptibility to Alzheimer's disease, heart disease and stroke," Kenney says. "Eventually, we believe the findings for the K haplogroup mtDNA will be applicable to other groups."

5 Easy Ways to Help DEF

Groundbreaking research such as the cybrid-model project needs your help to move forward. Try these easy ways to support DEF and its sight-saving research:

1. Shop using **smile.amazon.com** instead of amazon.com.
2. Celebrate events or honor others with a **tribute donation** to DEF.
3. Enjoy the ease of **monthly donations** charged to your credit card.
4. Maximize your gift by using your employer's **matching program**
5. **Donate a vehicle** in DEF's name.

For more details, visit **www.discoveryeye.org/other-ways-you-can-help**.

AMD.org DISCOVERY
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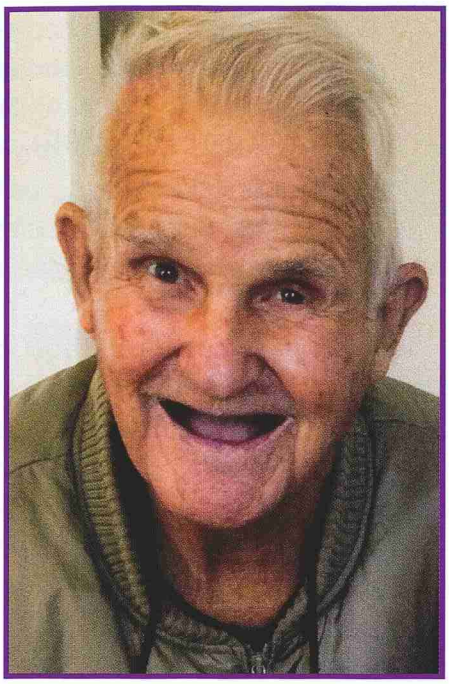
The Croquet-Playing Spectacle

A champion croquet player, CB Smith was known as much for his on-court antics as his world-class skill. *Croquet World Online* referred to him as an "unforgettable one-man spectacle," entertaining onlookers with his ever-present stuffed red parrot, flapping arms (his, not the parrot's), and unparalleled knowledge of the ins and outs of the game.



Born in Oklahoma, Smith and his adoptive family settled in Decatur, Ill., when he was in seventh grade. He joined the Navy straight out of high school and volunteered for submarine duty during World War II. His colorful stories of "killer runs in the Pacific" — and even more colorful stories of shore leave in Hawaii — culminated in an honorable discharge after three and half years of service. He married his high-school sweetheart, and the first of their five children was born two days after he left the Navy.

To support his growing family, Smith became a welder, working in the local steel mill for 30 years. His primary pastime was a game called "roque." An Olympic sport in the 1904 Summer Games, roque is described by *Croquet World Online* as similar to croquet, but in roque, "you play on a clay or dirt court with a low wall and bank balls through arches with a short-handled, two-faced mallet, one face made of a hard surface and the other of rubber." He won numerous national roque championships and traveled the country competing. One tournament brought him to Santa Monica, Calif., which he promptly nicknamed "heaven."

At age 56, he found himself newly retired, divorced and ready for a change. Smith headed to Santa Monica with a goal of playing plenty of roque. When he discovered croquet was much more popular in Southern California, he easily transitioned to croquet on the lawns of Roxbury Park in Beverly Hills. As a member of the Beverly Hills Croquet Club, he won numerous world championships, while entertaining other players, fans and students of the game.

Smith added card-playing to his repertoire, enjoying daily games of both croquet and poker for more than 20 years. "I was very popular with the ladies, mostly because I was a good dancer," Smith adds, though he decided to give up his "playboy ways" when he was in his 80s to marry his current wife, Naniek.

While driving on the freeway about four years ago, he noticed "the numbers on the other cars' license plates were zigzagging." He was diagnosed with age-related macular degeneration (AMD) in his right eye, in which he has lost all central vision. Smith gets regular Lucentis® injections at the Veterans Affairs (VA) West Los Angeles Medical Center, which seem to have halted or slowed the progression in his right eye; he has avoided wet AMD so far in his left eye.

"The VA has a good program for AMD, and I saw an ad for the Macular Degeneration Partnership (MDP) in the paper," he says. A regular attendee at the MDP support group in Santa Monica for the past two years, Smith likes to listen to the other attendees' stories and guest speakers.

Now 93, Smith still drives his car — against the wishes of several family members — as well as his electric scooter. While he has given up both croquet and poker in favor of his newest hobby, watercoloring books, he still loves to entertain, especially his 10 grandchildren and 10 great-grandchildren.

NKCF DISCOVERY
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The Guy with the Everlasting Grafts

Doug Beasley had to memorize his choir music. He was on a voice scholarship at the University of Central Arkansas. He couldn't see the music, so he had to sing from memory.

"In first or second grade, I got glasses and was told I was extremely farsighted," Beasley recalls. "After a few years, I didn't even need the glasses. I remember, vividly, going to the eye doctor in Houston in 1967, and I could see the Astrodome out his window. He said I had 20/20 vision in both eyes. I could see everything."

A year later, when the family returned to his hometown of Ft. Smith, Ark., 14-year-old Beasley was having trouble seeing the blackboard in school. Back to the eye doctor they went. This time, though, while his left eye was still 20/20, the optometrist couldn't refract Beasley's other eye. An ophthalmologist diagnosed him with keratoconus (KC) in his right eye. Two years later, his left eye followed suit. He was fitted with RGP contact lenses.

During high school, he says, "The Lord called me into the ministry, and said, 'I want you to be a music minister.' In the meantime, my eyes were getting worse."

In 1980, Beasley's right cornea "ruptured" — a condition called corneal hydrops — and he was put on a waiting list for a cornea transplant. Six weeks later, he underwent his first transplant. Two years later, he had a transplant in his left eye.

"When the sutures came out a year after my first transplant, they gave me contact lenses, and it was incredible," Beasley says. "I could see the leaves on the trees and the paths on the highway. Everything was crisp and clear. I had no idea my vision had deteriorated that badly since I was a teenager. I truly understood the bible passage, 'I was blind, but now I see.'"

In addition to his work as a music minister in several Baptist churches, Beasley has dedicated himself to eye-related causes, primarily through Lions Clubs International. He has served as president of several Arkansas Lions Clubs and on the board of directors of the Arkansas Lions Eye Bank and Laboratory. He is the recipient of numerous awards for his work and dedication.

"That's my way of saying thank you," Beasley says. "To thank those donors, I've done everything I can to promote the eye bank and Lions Club. I believe the Lord allowed this to happen so I could minister to people. I'm online with a lot of other KC people, on Facebook and elsewhere. And I help those people by telling them what happened to me."

"My grafts are still clear and healthy. I assumed they'd last my whole life. No one told me they were supposed to deteriorate after 20 years or so!"

Beasley discovered the National Keratoconus Foundation (NKCF) online in the late 1990s and offered to share his story to help inspire others. He was featured in the organization's newsletter in 1999 (www.bit.ly/nkcfbeasley).

Despite some setbacks, including premature cataracts caused by the steroids he took to combat transplant rejection, a vitrectomy and a "rubbing" retina that causes visual flashes, Beasley considers himself very "blessed."

"I went to a cornea specialist recently who said my cornea grafts — now 33 and 35 years old — are the oldest he's ever seen. They are still clear and healthy. I assumed they'd last my whole life," Beasley says. "No one told me they were supposed to deteriorate after 20 years or so! They call me 'the guy with the everlasting grafts.' I'm a walking miracle."

Vision-Enabling Technology

In just the past decade, the technology that has been developed to help people see is amazing. While medical research continues on promising treatments and potential cures, technologists have created ways to help people to see right now. We are excited about the possibilities presented by some of these technologies and are sharing just a few below. For more details on each of these technologies and others, visit our recent blog post at www.bit.ly/defvisiontech.

Argus II

In a healthy eye, photoreceptors (rods and cones) in the retina convert light into tiny electrochemical impulses that are sent to the brain, where they are translated into images. If the photoreceptors don't function correctly, your brain can't produce images. The Argus II Retinal Prosthesis System ("Argus II") from Second Sight is designed to bypass damaged photoreceptors.

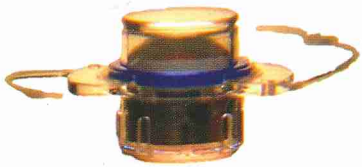
A miniature video camera housed in the patient's glasses captures an object. The video is sent to the small video-processing unit worn by the patient. This information is sent wirelessly to the antenna in an implant (which has been surgically implanted in the eye), then signals are sent to the electrode array that has been implanted on the retina, which emits small pulses of electricity. These pulses bypass the damaged photoreceptors and stimulate the retina's remaining cells. The visual information is then sent to the brain to create the perception of patterns of light, which patients can learn to interpret as objects.

eSight

While the Argus II is for people who have very little or no vision, the eSight is for people with low vision. eSight glasses require you to have a certain degree of remaining sight: If you can only see shadows, you likely don't have enough sight for the glasses to work.

Because most legally blind people retain limited sight concentrated in their peripheral vision, their eyes do not receive an adequate signal for the brain to recognize what is being seen. This can create blind spots, blurriness, inability to detect contrast and other symptoms that reduce vision. eSight is able to correct these issues by using a high-speed camera, video-processing software, a computer processor and video screens to project a real-time image on the inside of eSight glasses.

CentraSight



CentraSight's "Implantable Miniature Telescope" is for people with end-stage age-related macular degeneration (AMD). In end-stage AMD, the macula, where central vision occurs, is degenerated in both eyes without any healthy macular areas left for detailed central vision.

A tiny telescope — about the size of a pea — is implanted in one eye, behind the iris, where it works like the telephoto lens of a camera. It magnifies images onto the healthy areas of the retina to help improve detailed vision. The surgical procedure is only performed on one eye, because peripheral vision will be restricted in the implanted eye. The implanted eye uses the enlarged image to see things such as the "WALK" signs at a crosswalk, while the other eye is used for peripheral vision, such as checking to see if cars are coming from the side.

Blah, Blah ... Blog!

The DEF blog is full of useful tips, personal stories and up-to-the-minute information. Guest bloggers include leading eye doctors and researchers, as well as people sharing their own tales of coping with eye disease and the effects on their lives. Make sure you don't miss a thing by subscribing at **www.discoveryeye.org/blog**.

What Letter is Your Haplogroup?

(continued from front page)

Populations	Mitochondrial Haplogroups
African Origin	L
Native-American Origin	A, B, C or D
Asian Origin	A, B, C, D, F or G
European Origin	H, T, U, V, W, X, I, J or K

Similarly, most Ashkenazi Jewish populations (primarily those Jews whose families originated in Eastern or Central Europe) possess mitochondria of the K haplogroup. People with this haplogroup seem to be susceptible to a variety of age-related diseases, including AMD.

The incidence of AMD varies among different ethnic/racial populations. For example, in the United States, the likelihood of losing vision from AMD is very low for a person with an African maternal background, but it is much higher in people of European descent. Similarly, in an Israeli eye clinic, of the people who had AMD, 96 percent were Jewish, while only 4 percent were of Arab descent. This suggests that European mtDNA in retinal cells of Caucasians may be the reason they are more susceptible to AMD.

AMD is a complex disease. There are more than 30 genes associated with AMD, representing different biological pathways. Additionally, mitochondrial damage and specific mtDNA haplogroups have been associated with AMD. Finally, various environmental factors, such as smoking and obesity, increase the risk of developing AMD.

We still do not understand how to prevent dry AMD, which is the most common form of the disease. One major difficulty has been that when we study a diverse group of individuals, each with hundreds of different nuclear and mitochondrial genes, it is very difficult to identify the causes and pathways involved with developing AMD and determining effective treatments. One drug may not help everyone, and different people develop different types and severities of AMD.

In her research with different ethnic/racial groups, Kenney found that the Ashkenazi Jewish population (K haplogroup) is an excellent group in which to study age-related diseases. This group has very well-characterized nuclear and mitochondrial genes; the population tends to be relatively homogenous and to marry within their community. Finally, the Ashkenazi Jewish population has longevity, which increases the likelihood they will develop age-related diseases, such as AMD.

Kenney's laboratory created a "cybrid" test system (see "The Cybrid Model," inside), which uses cell lines with identical nuclei and nuclear DNA, but different mtDNA, so the differences in cell behavior can be attributed to the different mtDNA. Using the cybrid model, Kenney has compared cell behavior of mitochondria from subjects with the K haplogroup and the mitochondria from people of the H haplogroup, which is the most common European haplogroup. The study shows:

- Major differences in production of cholesterol and lipid molecules
- Altered levels of inflammation
- Differences in their responses to toxic effects of amyloid-β (a toxic protein associated with AMD and Alzheimer's disease)

These differences are important contributors to AMD and other age-related diseases. The findings show that maternally inherited mtDNA can influence how a person's cells respond to stress, which can contribute to age-related diseases. This is a completely new way of thinking about common aging diseases and offers new approaches to treatment and prevention of those diseases.