A Tale of Two Genes

Researchers find genetic variants that are linked to fatty liver disease — and the finding of the second variant helps confirm the significance of the first.

UT Southwestern researchers have identified two genetic variants that are strongly associated with accumulations of excess fat in the liver.

“About 30 years ago it was reported that some individuals developed what looked like alcoholic cirrhosis even though they didn’t drink alcohol,” said Dr. Jonathan Cohen, Professor of Internal Medicine and with the Eugene McDermott Center for Human Growth and Development.

Nonalcoholic fatty liver disease (NAFLD), as it’s known, is important because it’s widespread – as many as a third of U.S. adults could have NAFLD – and because it can lead to cirrhosis of the liver and liver cancer. The condition is related to obesity and insulin resistance, and is thus a burgeoning health problem because of the rise in obesity in the U.S.

To study NAFLD, the investigators used data from the Dallas Heart Study, a multiethnic, population-based study that gathered a variety of information on more than 3,000 participants, including DNA sampling and nuclear magnetic resonance spectroscopy, a quantitative noninvasive imaging technique used to measure the amount of fat in the liver.

One of the first curiosities the researchers noted was that the prevalence of fatty liver disease varied by ethnic group. It was uncommon among African-Americans, even in those who had high body fat, but was common among Mexican-Americans. This suggested that a genetic underpinning could be responsible, and prompted them to begin looking for genetic sequence variations that might be associated with the condition.

“Initially, we tested 9,229 DNA sequences – 9,228 showed no association. We were very excited by the 9,229th,” said Dr. Cohen.

That “outlier” gene sequence, the sequence that was strongly associated with liver fat content, was a variant of the PNPLA3 gene. Subsequently, the researchers showed that the same sequence variation also was associated with liver inflammation, cirrhosis, and liver cancer.

“This was exciting to us because it suggested that liver fat, per se, was not as benign as people had thought, but led to these diseases. We couldn’t exclude

Dr. Scott Grundy Honored for Leadership at Friends Event

At the fall 2015 meeting of the Friends of the Center for Human Nutrition, Dr. Scott Grundy, Professor of Internal Medicine at UT Southwestern, was presented with a commemorative black, Windsor-style chair honoring his more than three decades of leadership of the Center.

The chair is a physical representation of the funded chair named in his honor, the Scott Grundy Director’s Chair, currently held by the latest Director of the Center, Dr. Jay Horton.

In accepting the chair, Dr. Grundy thanked the Friends group for its generosity through the years. He also gave special thanks to Edith and Peter O’Donnell Jr. for their founding of the Center for Human Nutrition and the Friends of the Center, and for their immense support of the Center’s research.
Dr. Grundy Honored for Leadership at Friends Event

Since its inception in 1981, the Center for Human Nutrition has been under the direction of Dr. Scott Grundy. Now, I am honored to be chosen to follow Dr. Grundy in this role.

Dr. Grundy and members of the Center for Human Nutrition have made numerous scientific discoveries that have provided important insights into the causes of high blood cholesterol levels, and they have identified new ways to effectively treat high cholesterol levels to reduce the risk of having a heart attack. In fact, their efforts have significantly contributed to the remarkable 31 percent reduction in deaths attributed to cardiovascular disease over the past decade.

In more recent years, the research focus of the Center for Human Nutrition has expanded beyond cholesterol to include conditions associated with the metabolic syndrome—a disorder that is associated with obesity. The metabolic syndrome consists of a constellation of conditions that include high cholesterol, high triglycerides, low HDL, high blood pressure, high blood glucose, fatty liver, and a state of low-grade inflammation.

As a result, individuals with the metabolic syndrome have an increased risk of developing heart disease, stroke, diabetes, liver disease, and cancer. Inasmuch as alterations in the normal metabolism of nutrients are responsible for the development of the conditions associated with the metabolic syndrome, the Center for Human Nutrition is uniquely positioned to address this important clinical problem that affects approximately half of the U.S. population over the age of 60.

Moving forward, the Center for Human Nutrition will continue to be a conduit for basic and translational research in metabolism, but the role of the Center will broaden in the following ways:

1. Expand the basic and translational research investigator base, with a continued emphasis on obesity and metabolic disorders associated with the metabolic syndrome.

2. Develop and provide the infrastructure to facilitate interdisciplinary and collaborative research to speed the translation of basic scientific discoveries to the clinic.

3. Expand and create new mass spectrometry and nuclear magnetic resonance-based technologies for the study of metabolism in animals and humans.

4. Cultivate translational researchers who utilize basic scientific discoveries to develop hypothesis-driven studies in humans.

A new initiative will be carried out in collaboration with the Division of Digestive and Liver Diseases and the Department of Clinical Nutrition in the School of Health Professions. Together, we will develop a human nutrition program that not only carries out translational human nutrition research, but also one that can provide nutritional support and expertise for patients in our University Hospitals and Clinics.

To successfully accomplish our objectives, we will need to develop and recruit new talented investigators who fill important niches not currently represented at UT Southwestern or who have the potential to significantly augment areas of existing strengths. Training future basic scientists and clinical investigators has been a long-standing priority at the Center for Human Nutrition. As we expand the focus of our research, this important function will become even more critical.

UT Southwestern is blessed with a plethora of outstanding basic science investigators in metabolism. While each investigator has had significant individual successes, we have previously demonstrated that investigator productivity and impact can be enhanced significantly if there is a coherent mechanism to allow each to interact, collaborate, and use one another’s strengths to further develop their projects. I believe the Center for Human Nutrition can recapture this environment to bridge the interests of the existing basic scientists to not only enhance the individuals’ science, but also to facilitate the translation of their discoveries. In this end, we will continue to foster close alliances with existing Centers at UT Southwestern, including the Touchstone Center for Diabetes Research, the Division of Hypothalamic Research, the Eugene McDermott Center for Human Growth and Development, and the Advanced Imaging Research Center.

These alliances will facilitate the overall mission of the Center for Human Nutrition, which is to identify, train, and recruit new investigators to discover and characterize the underlying molecular, biochemical, metabolic, and physiological underpinnings that lead to human metabolic diseases. To accomplish our mission, we will build on the previous successes of the Center for Human Nutrition to cement UT Southwestern as the pre-eminent institution in metabolism research.

In more recent years, the research focus of the Center for Human Nutrition has expanded beyond cholesterol to include conditions associated with the metabolic syndrome—a disorder that is associated with obesity and consists of a constellation of other conditions.
The PCSK9-inhibitor Story

How UT Southwestern Medical Center researchers came to identify the PCSK9 molecule as a powerful target for lowering cholesterol

Last summer, headlines across the nation heralded a new class of drugs that has the ability to dramatically lower cholesterol levels — a class of drugs that grew out of groundbreaking research at UT Southwestern Medical Center.

All too often, approved by the U.S. Food and Drug Administration in July 2015, and evolocumab, approved by the FDA in August 2015, were the first two drugs in this new class known as PCSK9 inhibitors. A few years earlier, Dr. Helen Hobbs, Dr. Jonathan Cohen, and Dr. Jay Horton were making sometimes startling discoveries about the way the protein PCSK9 affects LDL cholesterol removal from the body. High levels of LDL cholesterol, the so-called “bad” cholesterol, are a major risk factor for heart disease. The work done by these researchers and their colleagues was the foundation stone on which these drugs were built.

“The lower cholesterol levels with mutations in PCSK9 found by Drs. Hobbs and Cohen, combined with the results of my lab studies in mice about how this molecule works, suggested that compounds that inhibit the PCSK9 protein could be a useful way to treat high cholesterol,” said Dr. Horton, Director of the Center for Human Nutrition.

The work of the three UT Southwestern scientists on PCSK9 began more than a decade ago when they speculated that the protein that codes for PCSK9 could be a good target for drugs to lower cholesterol. They hypothesized that other mutations in the PCSK9 gene would result in a loss of function.

“PCSK9 was targeted because it controls the activity of the LDL receptors in the liver,” said Dr. Cohen. “As rates of cardiovascular disease rose, there was an effort to find new drug targets in the immune system. The PCSK9 molecule was one of the attractive targets in the immune system.”

For their groundbreaking research, Drs. Hobbs and Cohen were awarded the 2015 Nobel Prize in Physiology or Medicine. Dr. Horton was awarded the 2014 Howard Hughes Medical Institute Distinguished Investigator Award.

Support of Friends Group Is a Family Tradition for John Levy

There are perks to being a member of the Friends of the Center for Human Nutrition, said John Levy, Chairman of the Friends group. If you’re wondering, for instance, if drinking coconut water can improve your cholesterol profile, just ask one of the distinguished scientists attending the next Friends Meeting.

Putting aside the perk of having your own scientific sounding board, for Mr. Levy, being a supporter of UT Southwestern’s Center for Human Nutrition is rooted in family. The Levy family has a long history of support for UT Southwestern, including funding two chairs: the Ruth W. and Milton P. Levy, Sr. Chair in Molecular Nephrology and the NCH Corporation Chair in Molecular Transport.

Mr. Levy’s father, Irvin Levy, was recruited by Peter O’Donnell Jr. to join the Friends of the Center for Human Nutrition when the group was formed in 1985. When the Junior Friends group was formed in 1992, Irvin Levy bought a membership for his son and daughter-in-law, Carol. “My father believed it was important for the next generation to get involved,” said Mr. Levy.

Before long, John and Carol Levy were members of the Steering Committee for the Junior Friends. At one point Mr. Levy chaired the Junior Friends, and two years ago he was named Chairman of the Friends of the Center for Human Nutrition.

As proud as Mr. Levy is of his family’s longtime support of UT Southwestern, as a fifth-generation Texan he also is proud of his deep Texas roots. In 1919, Mr. Levy’s grandfather, Milton Levy Sr., founded the National Disinfector Co. in Dallas. Mr. Levy grew up in Dallas and then attended the University of Texas in Austin. While living in the Dobie dorm his freshman year, Mr. Levy met his wife, Carol Rosenfeld, who hailed from Houston.

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Calciuim Supplements Can Help Maintain Bone Health—Just Don’t Go Overboard

Some 10 million Americans have osteoporosis, and another 40 million have low bone mass and are at risk for developing osteoporosis, a dangerous thinning of the bones that is particularly common in postmenopausal women. Pair that with the difficulty of consuming recommended levels of calcium (1,200 milligrams a day for women over age 50) while maintaining some semblance of calorie control, and it’s obvious why many women turn to calcium supplements.

Dr. Naim Maalouf, Associate Professor of Internal Medicine and an endocrinologist who specializes in bone diseases and mineral metabolism, said about half the women he sees in his practice don’t consume enough calcium. For those women, he recommends increasing their consumption of dairy products and, if they can’t get enough calcium from food, taking a calcium supplement. However, Dr. Maalouf said a small minority of his patients—about 5 percent—go to extremes with calcium supplements and consume more than 2,000 milligrams of calcium a day, which can be a problem.

Clinical trials offer stronger evidence than observational studies, but Dr. Maalouf said the results of the only clinical trial to study calcium supplements and heart disease were also not clear-cut.

One thing has been clear, however: “It’s really only with higher intakes of calcium that there is potentially a problem,” said Dr. Maalouf. So that makes it easy for Dr. Maalouf to give advice to his patients: Pay attention to the amount of calcium you consume in both food and supplements, and get as close as you can to the recommended daily levels for your age and sex, but don’t exceed the recommended levels.

The two calcium supplements that are recommended are calcium carbonate, which must be taken with food, and calcium citrate, which can be taken with or without food. When you calculate your daily intake of calcium, don’t forget to include the calcium in the food you eat and in the multivitamins you consume. Dairy foods are the best sources of calcium, with leafy, green vegetables like spinach and kale also supplying a smaller amount of calcium. To determine how much calcium is in a serving of packaged food, look at the percentage of daily calcium listed on the label and then add a zero. For example, if a frozen pizza package says a serving supplies 15 percent of the daily recommended calcium intake, that means a serving supplies 150 milligrams of calcium.

The recommended daily calcium intake for men and women ages 19-50 is 1,000 mg/day. For men ages 58-70, the recommended daily calcium intake is 1,000 mg/day. For women older than 50 as well as men older than 70, the recommended daily calcium intake is 1,200 mg/day.

Dr. Maalouf holds The Frederic C. Bartter Professorship in Vitamin D Research.

Recently, the question has been raised as to whether calcium supplements might contribute to atherosclerosis, or the development of calcified plaques in the arteries that supply blood to heart muscle. “The problem is that there is no definite answer to this question,” said Dr. Maalouf. “Some observational studies have suggested calcium supplements can increase cardiac events, while other observational studies have found a reduction in cardiac events.”
Join the Friends

Becoming a member of the Friends of the Center for Human Nutrition makes you part of the effort to improve health and quality of life today and into the future. Your membership will support the projects of promising young scientists and ensure that rigorous nutrition research continues. Your membership also entitles you to receive invitations to attend regular presentations from distinguished scientists in disciplines affected by nutrition, including heart disease, diabetes, and obesity. All members receive the Center for Human Nutrition Newsletter and other communications.

Annual membership in the Friends is a tax-deductible contribution starting at $1,000 per individual or couple. Membership in Younger Friends, which has activities oriented toward those under 45 years old, costs $250 for those up to age 40, and $500 for those 41 to 45 years. To join the Friends, call 214-648-2344 or email giving@utsouthwestern.edu.

Upcoming events:

**April 27:** Annual spring meeting of Friends of the Center for Human Nutrition with speaker Dr. Samuel Klein, Director, Center for Human Nutrition, Washington University – 4 p.m., in the T. Boone Pickens Biomedical Building.

**June (date to be determined):** Seminar on the health benefits of wine.

The Center for Human Nutrition Newsletter is published by the Center for Human Nutrition at UT Southwestern Medical Center.

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