Central Core Disease

In Focus

CCD: A Disease with Many Faces

by Margaret Wahl

Forty-one-year-old Sandy Doak remembers that she was never athletic, couldn’t do sit-ups, and always had trouble finishing physical tasks. But, she says, “I never really thought I had anything wrong. I just thought I was awkward. I knew I was weaker than others. That had pretty much lasted most of my life.”

Sometimes she found herself the object of ridicule, which, while friendly, wasn’t exactly welcome. “The joke around my office when I was in my 20s was, ‘Let’s watch Sandy jump,’ and I’d jump, and my feet would not leave the floor, and we’d all laugh about it.”

A few years ago, at Doak’s office in St. Louis where she administers insurance claims for members of a carpenters’ union, a physical fitness expert visited and estimated everyone’s body fat percentage. Much to everyone’s surprise, since Doak is 5 feet tall and weighs 128 pounds, the test result said her body was 38 percent fat. There was only one way that could be the case, the fitness expert and she agreed: She had very little muscle. For Doak, it was a clue that something was really wrong.

For others, clues that something is wrong come much earlier and are harbingers of very severe problems.

By the time Jared Earlenbaugh of Reno, Texas, was 2 years old, his mother, Alexia Zuege, suspected something was wrong because he wasn’t running around like other children his age. In fact, he never ran at all and when he walked it was more of a “side-to-side waddle,” Zuege recalls. Falls caused a broken hip at age 3 and a broken collarbone at age 4.

Now a junior in high school, Jared uses a wheelchair, needs a ventilator to

Fast Facts

Central core disease (CCD) is a genetic muscle disease characterized by the appearance of corelike structures running through the centers of muscle fibers. The cores are areas of metabolic inactivity.

Symptoms vary widely in severity and can begin anywhere from infancy to adulthood. They include weakness, muscle cramps, orthopedic abnormalities (spinal curvature, foot deformities, hip dislocations) caused by the weakness, and a dangerous susceptibility to malignant hyperthermia, an adverse reaction to anesthesia.

The disease is usually dominantly inherited, meaning only one gene mutation, inherited from one parent, is necessary to cause symptoms.

The underlying molecular cause of the disease is an abnormality of calcium release from deep inside the muscle fibers. Normally, a signal from a nerve fiber tells a muscle fiber to contract and, after a cascade of events, calcium is released in a burst from internal storage areas. Calcium is then pumped back to the storage areas until the next contraction.

Some of the approximately 50 disease-causing defects so far identified in the internal calcium release channel (the ryanodine receptor) cause abnormal leakage of calcium into the fiber and depletion of internal calcium stores. Others cause a blockage of calcium release.

MDA’s current commitment to research in CCD, as of Jan. 25, 2010, is $1,156,989, spread over seven grants.
breathe, and can eat only through a feeding tube that bypasses his weak swallowing muscles.

Despite their different medical histories, Sandy Doak and Jared Earlenbaugh share a diagnosis, the genetic muscle disorder central core disease, or CCD. The disease takes its name from structures in the center of many muscle fibers that appear empty, or “cored.”

Varied symptoms, some commonalities

There probably is no such thing as a typical case of CCD, says Susan Iannaccone, director of pediatric neurology and the MDA Clinic at Children’s Medical Center in Dallas.

“There’s a wide variation. There’s a severe infantile and a more typical juvenile presentation, and there are adults who have it who are completely asymptomatic,” says Iannaccone, who also is a professor of neurology and pediatrics at the University of Texas Southwestern Medical Center.

“An infant with the severe form of the disease is going to be a ‘floppy’ infant and may have difficulty swallowing and breathing. These babies may require a lot of technological support early in life,” says Iannaccone. The condition of these babies frequently improves and their dependence on technology such as feeding tubes and ventilators decreases. But, Iannaccone says, there is no “100 percent certainty” of improvement.

Children who do improve generally reach their typical motor milestones, although these may be delayed, with walking achieved between 3 and 5 years of age. However, she cautions, “There’s a lot of variation on that theme.”

The juvenile presentation of CCD can also vary widely, she notes. Children may not have severe difficulties in infancy but may have some delays in meeting motor milestones and may not walk until they’re between 19 and 21 months old. (Seventeen months is considered the upper limit of the normal age range for walking, and most healthy children walk at around a year.)

Children with CCD who weren’t severely affected in infancy tend to be skinny, perhaps because they have to expend extra energy getting around and perhaps because their chewing muscles may be somewhat weakened. They may have an abnormal gait, with difficulty climbing stairs and getting up from the floor. “There may be some facial weakness and droopy eyelids,” Iannaccone says.

At the lowest end of the severity spectrum are some adults who are said to have CCD because of the appearance of their muscle biopsy samples, but who have minimal or no muscle weakness.

Despite the variations, there are some commonalities in CCD.

Muscle cramps seem to be a “common complaint across the board” for people with CCD, Iannaccone says. Also, CCD does not affect intelligence. “It’s purely a motor problem,” she notes.

Another important feature of this disease that has to be considered no matter how severe or mild the case is a susceptibility to a severe adverse reaction to general anesthesia. For more on this condition, see “Malignant Hyperthermia,” page 6.

‘Apples and oranges’

Brian Tseng, director of the pediatric neuromuscular service at Massachusetts General Hospital in Boston, where he also codirects the MDA clinic, says children are usually referred to him because they have weakness, low muscle tone or orthopedic problems, including abnormal positioning of the spine, feet or hips. The apparent bone problems, he says, are secondary to the muscle weakness, although you can’t always tell that at first glance.

 Babies who come to him generally have very low muscle tone and may be seriously ill because of weak respiratory or sucking and swallowing muscles. “They’re vulnerable [to serious illness] due to respiratory and feeding issues,” he says.

But, Tseng notes, there are other children whose onset of CCD symptoms is in childhood or adolescence, and with these children, “you’re talking apples and oranges compared to the infant-onset form, even though their muscle biopsies may look very similar.”

Tseng says CCD is generally considered “nonprogressive,” but he finds that’s true only about 90 percent of the time.

The typical older child or adolescent who receives a CCD diagnosis may have been a somewhat floppy baby who reached his or her motor milestones, such as walking, a little bit late.

“They didn’t get medical attention until maybe their teens, when they began having trouble keeping up with their peers or couldn’t go on hikes or ride their bikes,” he says. “They have low muscle tone, mild weakness and may have muscle cramping during or after exercise.”

If a doctor carefully reviews the child’s history, Tseng says, the child “may have had some subtle problems earlier, but not enough for the parents to seek medical attention. The child was probably just a kid who compensated and settled into more sedentary activities. They’re generally all cognitively normal, and many are very bright.”

An even milder presentation of CCD can be seen in those who receive a diagnosis in adulthood, Tseng says. Some adults may come to the attention of medical professionals only after they have a child with symptoms of CCD or when they take part in a CCD research study as seemingly unaffected family members. Some may only have a spinal curvature or an abnormally high level of the muscle enzyme creatine kinase on a blood test, indicating some degree of muscle destruction is going on, but not necessarily enough for the person to notice it.
“This variation could be a fertile area to better understand the factors that enable some individuals with CCD to be less affected than others with more severe CCD,” Tseng notes.

Tseng says CCD is generally considered “nonprogressive” (doesn’t get worse), but he finds that’s true only about 90 percent of the time. “There are people who could once walk but then stop walking,” he says.

On the other hand, Tseng has seen some patients improve with time. “You have to be careful about generalizing, extrapolating from the literature whenever discussing an individual child or adult with CCD; each person is unique in amazing ways if you look carefully.”

Managing the disease

There are no specific treatments for CCD, but there are some things people can do to manage their disease and some precautions they should take.

Avoiding an episode of malignant hyperthermia during surgery is number one on the list for Iannaccone.

“The first thing I tell parents is that their child should never have any surgical procedure outside a pediatric specialty hospital, and that includes dental procedures,” says Iannaccone, who also recommends a medical ID tag that indicates the patient’s diagnosis and the contact information for his or her doctor.

Muscle cramps and pain are troublesome for many people, Iannaccone says, and they can be prevented to some extent with stretching exercises. “Cramps are usually in the weight-bearing muscles, the calves and thighs,” says Iannaccone, who recommends patients consult with a physical therapist before doing stretching at home.

Iannaccone also recommends consultations with a nutritionist to make sure patients are getting enough fluid, potassium and calcium, because a lack of any of these can contribute to cramping episodes.

For muscle pain, she recommends the anti-inflammatory medication ibuprofen, which can be purchased over the counter, and also encourages massage and warming of the muscles (such as in bathwater).

“We always write recommendations for schools that include the fact that the child should be allowed to stop and rest if they’re having cramps or feel tired,” says Iannaccone, who says she encourages patients to listen to their bodies and respond to those messages.

“In junior high and high school, they often need extra time to get between classes, and they may need two or three sets of books so they don’t need to carry books around.”

Although she doesn’t have data to prove it, Iannaccone says she believes that, for people with CCD, “pain is not gain.”
Normal is Overrated

When Jared Earlenbaugh was 2 years old, he “wasn’t running around driving his parents nuts” the way his mother, Alexia Zuege, had expected. However, he was her first child, born when she was only 19, and she didn’t think too much about it.

But as other children mastered walking, running and other motor skills, Jared developed a side-to-side waddle, never ran, could only get up from the floor by holding onto the furniture, and fell down a lot.

He had his first muscle biopsy at age 3, which “came back undiagnosable,” Zuege says, and then another one at age 5, which doctors interpreted as showing a muscle disease called centronuclear myopathy, which turned out to be the wrong diagnosis.

Jared, meanwhile, was walking “with his butt sticking out and his chest forward,” began developing a spinal curvature, and was frequently ill with respiratory infections. During one year, he had pneumonia six times.

In 1999, Zuege moved to Texas and took 6-year-old Jared to see pediatric neurologist Susan Iannaccone in Dallas. Iannaccone, who now directs the MDA Clinic at Children’s Medical Center of Dallas, admitted Jared to the hospital to fight another bout of pneumonia and recommended another muscle biopsy.

In the spring, the muscle biopsy was done, and “that’s when they diagnosed him with central core disease,” Zuege recalls, adding that Iannaccone said Jared’s CCD was among the worst cases she had ever seen.

Jared’s swallowing muscles were so weakened that he was frequently inhaling food and liquid into his lungs, a major risk factor for respiratory infections. “In March 2000 they did a g-button [type of feeding tube] placement,” his mother recalls, ending his days of oral eating and drinking.

Then, in 2001, at age 7, Jared underwent surgery to remove the middle and lower lobes of his right lung, which had been scarred beyond repair from the many pneumonia episodes. And, the following year, he underwent a tracheostomy and began using a portable ventilator.

“Ever since the trach, he has not been hospitalized for pneumonia,” Zuege says. Jared also uses a CoughAssist, a device that helps pull mucus out of the respiratory tract. Zuege calls it a “miracle worker.”

“It gets the stuff right up out of his chest,” she says, “It saved his life a few times. We take it everywhere. If it wasn’t for getting out plugs and secretions, he would probably be sick a lot.”

As for Jared, who didn’t start school full time until fifth grade because of constant illnesses, he’s now a junior in high school and doing well. “He’s smart as a whip,” his mother says. “But he’s behind in school because of being out with so much illness.”

He has a modified school day, lasting from 10 a.m. to 2:30 p.m., part of which he spends in regular classes and part of which he spends in resource classes to help him catch up.

Although his mother would like him to think about his education after high school, Jared prefers playing video games to thinking about college admissions. “I just want to stay home and play games,” he says, “but my mom wants me to have a future, so I guess that’s out of the question.”

The hardest part about his CCD, he says, is not being able to eat or drink by mouth, although he’s allowed what’s known as “recreational tasting.” Zuege describes this as offering “a bite smaller than what you would give an infant, because you don’t want to overstimulate the salivary glands and cause more secretion.” Jared says his feeding tube formula, Jevity, “keeps me from withering away,” but it’s no substitute for his mother’s “awesome spaghetti.”

Zuege says, “For the most part, he’s a happy-go-lucky kid, although he has much to deal with.” She offers a recent statement made by Jared — “Being normal is overrated” — as a good example of his attitude. “He takes things in stride for the most part,” she says. “He’s been through a lot and never really complained.”

Jared says he depends on other people “to get me dressed and get my treatments,” but that he does a lot for himself. His advice to other kids in his situation is: “Love yourself, and don’t ever stop loving yourself.”

At 3 months, Jared Earlenbaugh’s motor skills appeared to be typical, although problems would become apparent by age 2. At 16, he requires a trach, feeding tube and power chair. His dachshund, Sierra, doesn’t seem to mind.
Surprised by Progression

“In my opinion, I’ve progressed a lot,” says 41-year-old Sandy Doak, who saw little progression of her central core disease until about five years ago, when she was in her mid-30s. “I didn’t have muscle spasms years ago, and I didn’t have these aches that I have. I’m a very active person, and I’ve been experiencing fatigue that I’ve never experienced.”

Doak lives in Imperial, Mo., with her husband and three children and processes medical claims for the carpenters’ union in an office in St. Louis.

She’s not the only person in her family who’s affected by this genetic disease. “When I was in my 30s, I started having discussions with my brother and sister,” she says, “and they too were experiencing some things. It was the first time I had ever heard that my brother could never do a sit-up.” Her brother has two children, one of whom, at age 14, also was beginning to have some muscle problems. “They had to put her bedroom on the first floor,” Doak recalls.

“We believe that my grandfather, my dad’s dad, had the disease. Looking back, I remember him having difficulty with getting up from sitting positions, walking with a cane, and having difficulty with steps. We believe that, out of nine of his children, he passed it to my father and one sister of my father. That sister is now deceased, but I know she also had the issues that we all struggle with.”

Five years ago, Doak and her husband built a new, two-story house. “I was having difficulty with steps,” she recalls, but nothing severe enough to make her think twice about building a house with a staircase.

“But something happened to me about five years ago, and I’ve just progressed significantly compared to what I did in the last 30 years,” she says.

“I would never have bought a two-story house had I known that I was going to be doing what I’m doing now. I used to be able to go up steps and kind of fake it. My legs would hurt and burn. I would go up with somebody behind me, and they would say, ‘Are you limping a little bit?’ But now I have to send everybody up ahead of me and go up like I’m 90 years old. I go up very slowly. I have to hold on and crawl up the rest of the steps.”

In January 2010, Doak visited the MDA Clinic at Washington University in St. Louis and talked with neurologist Alan Pestronk, the clinic’s director, and other professionals, including a physical therapist. She learned that what she had been told earlier by another doctor — that she could exercise as much as she wanted in whatever way she wanted — might not have been good advice.

Much to her dismay, she learned that a combination of frequent stair climbing and regular use of an elliptical trainer, which she thought was building muscle, might actually have been destroying it. She’s planning to work with the doctors and therapists at Washington University to modify her approach to exercise.

The disease now seems to be progressing to include her upper body, whereas earlier it mainly affected her legs. Fixing her hair, cutting her son’s hair, and even resetting the buttons on the car radio have become problematic. “My arms fatigue and I have to stop what I’m doing and rest.”

Doak realizes there are many people with muscle diseases who are far worse off than she. “But,” she says, “In my mind, I used to be able to do things that now I can’t. It’s still bothersome.”
In 1960, the medical journal The Lancet published a sobering report of a 21-year-old student whose broken leg required surgical repair but who was less concerned about his leg than the risk of general anesthesia. He told his doctor that, since 1922, 10 of his relatives had died as a direct result of inhaled anesthesia. The young man ended up having surgery on his leg and surviving an episode of what would later be called “malignant hyperthermia” (MH), a reaction to certain anesthetics that leads to uncontrolled muscle contractions, accelerated metabolism, high fever, and all too often, if not treated, death.

The 1960 report markedly increased awareness of the phenomenon, which, even as late at 1976, still carried an estimated mortality rate of 28 percent.

The disastrous phenomenon appears to be caused by uncontrolled leakage of calcium from inside muscle fibers. It’s particularly common among people with central core disease, although it also occurs in people who don’t have CCD.

According to the Malignant Hyperthermia Association of the United States (www.mhaus.org), the inhalation anesthetics that can trigger MH include sevoflurane, desflurane, isoflurane, halothane, enflurane and methoxyflurane. In addition, the muscle relaxant known as succinylcholine (brand name Anectine), a “depolarizing” relaxant often used with anesthesia, can also trigger the response.

MHAUS lists as safe for people with MH susceptibility (MHS) all local anesthetics, as well as the anesthetics and pain relievers nitrous oxide, barbiturates, narcotics, propofol, benzodiazepines, ketamine and etomidate. It lists the “nondepolarizing” muscle relaxants pancuronium, cisatracurium, atracurium, mivacurium, vecuronium and rocuronium as safe for use in people with MHS.

Surgery can be safely performed on people with MHS, but it’s important that the surgical team avoid the triggering agents and use the safe agents.

If an MH episode should occur, it must be identified and treated early in its course with intravenous dantrolene (Dantrium) and immediate supportive care in the operating room. Dantrolene, available in the United States since 1979, can stop an MH episode by interfering with muscle contraction, probably by blocking the release of calcium from inside the muscle fiber.

MHAUS doesn’t, however, recommend preventive treatment with dantrolene, and cautions that the drug can make muscle weakness worse in people with muscle disease.

Everyone with CCD is potentially susceptible to MH and should take appropriate precautions with surgery. Family members who seem unaffected by CCD could be MH-susceptible and should assume they are until proven otherwise by a muscle biopsy or genetic test.

MHAUS considers a caffeine/halothane contracture test (CHCT), performed on a muscle biopsy sample, to be the “gold standard” to diagnose MHS. False negatives (a determination that the person is not susceptible to MH when he really is) are rare, although false positives (a determination that someone is susceptible to MH when he really isn’t) are frequent, occurring about 20 percent of the time. MHAUS provides a list of centers capable of performing CHCTs.

The primary, but not the only, genetic cause of MHS is any of a number of mutations in the RYR1 gene, some of which also cause CCD. To be on the safe side, it’s wise to assume that any CCD-causing RYR1 mutation is a potential MHS mutation.

Importantly, MH reactions don’t always occur with the first exposure to inhaled anesthesia, so one event-free surgery is no proof that one does not have MH susceptibility.

**Genetic Testing for CCD and MHS**

Genetic testing for CCD is not yet widely available outside research studies. Commercial testing that includes analysis of the entire RYR1 gene is available at:

**Prevention Genetics**
3700 Downwind Drive
Marshfield, WI 54449
(715) 387-0484
www.preventiongenetics.com
clinicaltesting@preventiongenetics.com

The company requests that it be contacted only by health care providers, such as a personal physician.

DNA testing for malignant hyperthermia susceptibility (MHS) is somewhat more widely available. In addition to Prevention Genetics, genetic testing for MHS is available at two locations:

**University of Pittsburgh Medical Center Division of Molecular Diagnostics**
(412) 648-8519

**Toronto Medical Laboratories**
(416) 340-4688

Both these laboratories request that they be contacted only by health care providers.
Getting to the Core of CCD
Much progress but mysteries remain

by Margaret Wahl

Back in 1956, investigators at the National Institutes of Health described five members of a three-generation family, all of whom had experienced delayed motor development, with walking not achieved until age 4 or 5, and difficulty climbing stairs, running and changing from a back-lying to a sitting position.

Each of them underwent a biopsy of a thigh muscle and, in every case, the samples showed a previously unknown type of abnormality. If the muscle fibers were viewed in cross-section, areas that appeared to be almost amorphous (formless) could be seen in the central part of the fibers — a few muscle fibers in one case and almost every fiber in the other four cases. Viewed from the side, the amorphous areas ran almost the entire length of the fiber (see illustrations, below).

By the 1960s, the muscle disorder had received a name based on this phenomenon: central core disease. The cores were found to be devoid of metabolic activity and to lack crucial energy-producing structures called mitochondria.

It makes sense that metabolically inactive areas of muscle fibers would lead to problems with muscle function but, mysteriously, the number of cores isn’t well correlated with disease severity. Some people who have cores in almost all their fibers are minimally affected, while others, with few cores, are very weak.

The picture is further complicated by the fact that most people only undergo one or two muscle biopsies, so any change in the number or nature of the cores over time can’t be observed. In addition, any particular biopsy sample taken at a given time might not be representative of all the muscles.

A complicated dance

Although they disagree on the details, most experts believe cores reflect poor regulation of calcium inside muscle fibers, a conclusion that results from decades of study of muscle physiology, particularly the process called “excitation-contraction coupling” that underlies muscle movement and relaxation.

This process is a complicated dance involving the ebb and flow of many charged particles (ions) across the membrane that surrounds muscle fibers and, in the case of calcium ions, into and out of internal storage areas deep inside the fibers. (See “How Ion Channels Regulate Muscle Contraction,” page 8.)

“Excitation” refers to the process by which muscle fibers are stimulated by nerve fibers, and “contraction” refers to the process by which microscopic filaments inside each muscle fiber slide over each other, causing muscles to shorten, or contract.

It’s been known since the 1990s that malfunctions of the internal calcium release channel are the basic cause of most cases of CCD. But even now, the precise interactions among calcium release, calcium levels, core formation and muscle malfunction are not completely understood.

Identifying the calcium release channel

In the early 1980s, says muscle biologist Sidney Fleischer, “Researchers in the field were interested in diseases of muscle, but we didn’t know much about the molecular machinery.”

Researchers knew that a rise of calcium concentration in the main compartment of the muscle fiber is the messenger that triggers muscle to contract, and that uptake of calcium from the main part of the fiber back into the storage areas enables muscle to relax, says Fleischer, who received MDA funding to study muscle membranes back then, and who has since retired from his position as a professor in the department of molecular biology at Vanderbilt University in Nashville, Tenn.

Researchers also knew that when muscles relaxed, a molecular pump moved calcium ions into the internal storage compartment, and when muscles contracted, somehow calcium was released from this storage depot into the main compartment of muscle fibers.
However, researchers did not know what mechanism governed this release of calcium during contraction, says Fleischer.

Fleischer and many other scientists — particularly David MacLennan at the University of Toronto in Canada and Kevin Campbell at the University of Iowa (both of whom have received MDA support) — ultimately were able to decipher the calcium release mechanism.

It’s now understood that the internal calcium release channels in a muscle fiber — the “ryanodine receptors” — open in response to signals from different calcium channels, located on special indentations of the muscle fiber’s surface. These surface channels act as sensors of voltage changes.

The internal release of calcium through the ryanodine receptor is the next-to-last step before muscle contraction can occur. It allows calcium ions to surge out from the storage depots and combine with filaments in the fiber that slide over each other, causing muscle contraction.

If the channel doesn’t close back up again almost immediately, calcium will continue to leak out, leading to a prolonged muscle contraction; and the internal calcium stores will become depleted, leaving insufficient calcium for the next contraction.

**Enter the geneticists**

By the early 1990s, scientists had begun speculating that disorders of calcium release in general, and of the ryanodine receptor in particular, might underlie both central core disease and a dangerous reaction to inhaled anesthesia and certain muscle relaxants known as “malignant hyperthermia susceptibility,” or MHS.

Malignant hyperthermia — which affects many people who have CCD as well as many who don’t — is a phenomenon of prolonged and extreme muscle contraction and very high temperature elevation (hyperthermia) in response to halothane-type inhaled anesthetics and so-
called depolarizing muscle relaxants, such as succinylcholine, often given during surgery. (See “Malignant Hyperthermia,” page 6.)

In 1992, researchers had linked at least some cases of malignant hyperthermia susceptibility to mutations in the RYR1 gene, which carries instructions for the ryanodine receptors in skeletal muscles.

Then, in 1993, MacLennan’s group in Toronto and a separate group of European investigators linked mutations in RYR1 to CCD. Some of the RYR1 mutations cause both disorders, and some appear to cause only one or the other. However, it’s not possible to tell for certain whether or not someone is susceptible to MH if an anesthesia-related reaction hasn’t been experienced. (Susan Iannaccone advises anyone with an RYR1 mutation or a mutation in another gene, known as SEPN1, to assume he or she is at risk for MH.)

Today, some 50 mutations in RYR1 have been found to cause CCD. Most are inherited in a dominant fashion, meaning a child needs to inherit the flawed gene from only one parent to show the disease. Occasionally, CCD appears to be inherited in a recessive pattern, meaning a gene mutation from each parent must be inherited before the disease manifests itself in a child.

Mutations in RYR1 that cause CCD can result in either leaky calcium channels, which lead to depletion of calcium from the internal stores and excess calcium outside them; or an inability of the calcium channel to open in response to voltage changes, known as “excitation-contraction uncoupling.”

Cores still a mystery

“The first RYR1 mutations discovered caused calcium leaks,” says muscle biologist Susan Hamilton, a longtime MDA research grantee who specializes in the ryanodine receptor and calcium release.

Scientists, looking for an explanation of the formless “core” that characterizes the disease, hypothesized that a calcium leak might cause a calcium overload, destroying the mitochondria in the center of the muscle fiber but not the mitochondria on the periphery of the fiber, which has systems to deal with calcium overload, explains Hamilton, a professor in the department of molecular physiology and biophysics at Baylor College of Medicine in Houston.

“But lo and behold,” says Hamilton, “other mutations in RYR1 create a block in the channel instead of a leak, so there’s less calcium leaking out, not more.”

As a result, she says, researchers have had to go back and review what they know about core formation. “We don’t know why cores form, and that’s the emphasis of a lot of research.”

In 2009, Hamilton was part of a study in which investigators inserted an RYR1 gene mutation into mice and observed the formation of cores in their muscle fibers over time.

They say they think the mice will provide a powerful new tool for investigations of muscle diseases like CCD.