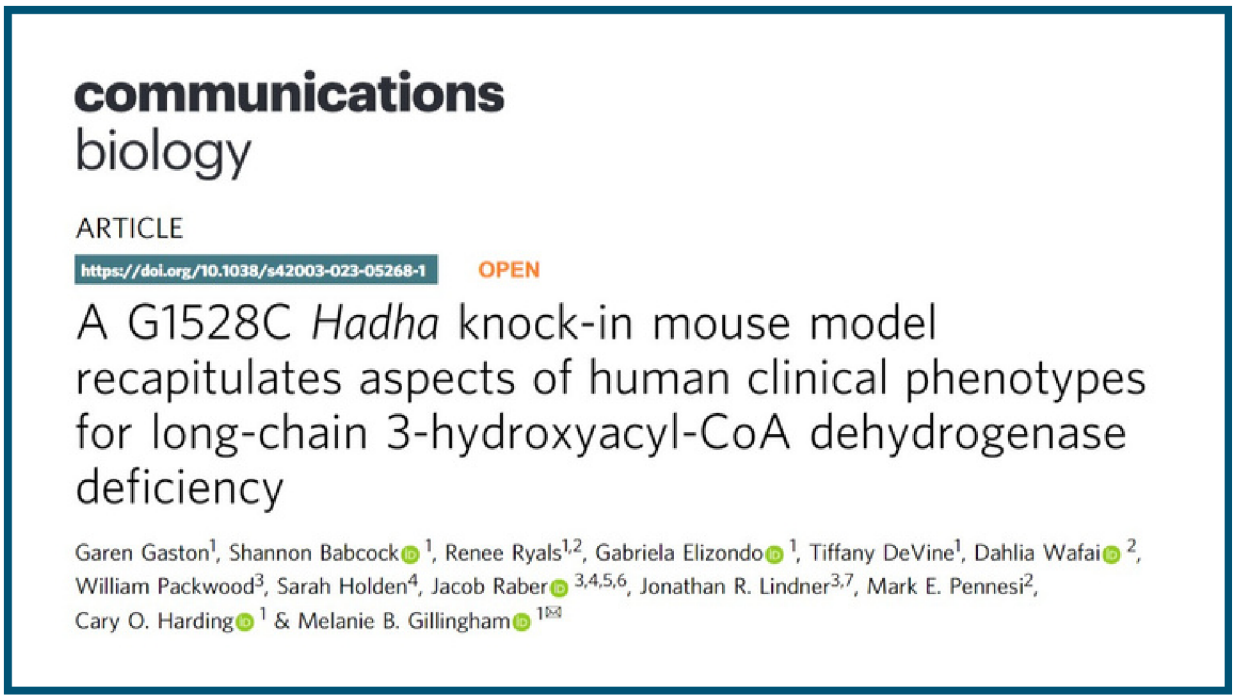
FALL/WINTER 2023

Gillingham Lab

RESEARCH NEWSLETTER

NEW PUBLICATION!



We have a new article published in the journal, Communications Biology. The title of the article is "A G1528C Hadha knock-in mouse model recapitulates aspects of human clinical phenotypes for long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency" and can be found online at **https://doi.org/10.1038/s42003-023-05268-1**.

The article details the development of our novel LCHADD mouse model. We used a gene editing technique called CRISPR to put the common LCHADD mutation, G1528C, into mice. LCHADD mice were studied to see if they developed similar symptoms to humans with LCHADD. LCHADD mice exhibited similar features of the human disorder, including impaired fatty acid oxidation, elevated acylcarnitines, low fasting blood ketones, impaired motor function, exercise intolerance, dilated cardiomyopathy and impaired eyesight due to retinal dysfunction. The development of an effective LCHADD mouse model allows us to further study the various complications of LCHADD and to test new therapies.

LCHADD CARDIOMYOPATHY

The term cardiomyopathy means there is a disease affecting the heart muscle (cardio=heart; myopathy=disease of the muscle). Cardiomyopathy has been a relatively frequent finding in fatty acid oxidation disorders (FAOD) observed in approximately 30 to 50% of patients. Different types of cardiomyopathy vary in severity and type, even among people with the same molecular diagnosis. Some cardiomyopathies are characterized by a large heart with impaired blood pumping activity (Dilated Cardiomyopathy, DCM), some are associated with a large heart but small chamber size and reduced filling of the heart with blood (Hypertrophic Cardiomyopathy, HCM) and some can be decreased filling of the heart with blood (Restrictive Cardiomyopathy, RCM).

Arrhythmias are abnormal electrical signals in the heart that signal the heart to beat. Arrhythmias are also reported in people with a FAOD diagnosis, including people with LCHADD. In a study of 107 participants with FAOD, 24 had arrhythmias (22%). These arrhythmias vary a lot, even among people with the same genetics. Commonly reported arrhythmias are premature ventricular contractions (PVCs) which are extra heat beats that occur randomly and sporadically, ventricular flutter, supraventricular tachycardia, and other conduction anomalies like AV blocks.

These are abnormal electrical signals usually detected by an electrocardiogram (ECG) that can come from the atria or the ventricles and vary in duration and severity. Most are of short duration and have no or only minor symptoms, like palpitations. Rarely, they can cause light-headedness, dizziness, and even loss of consciousness. Some may progress to life-threatening arrhythmias like ventricular tachycardia and ventricular fibrillation.

While cardiomyopathy among infants is a well-recognized complication of childhood LCHADD, little is known about its progression. Thanks to the newborn screening program across the world, early diagnosis and intervention have reduced infant death from cardiomyopathy significantly. Many infants with cardiomyopathy survive and this condition usually resolves during early childhood. Children with LCHADD often have normal cardiac function and electrical signals on exam.

CARDIAC COMPLICATIONS IN ADOLESCENTS AND YOUNG ADULTS

Over the past several years, reports of sudden cardiac arrhythmias resulting in cardiac arrest and death have come up in our young adult LCHADD community.

Sudden cardiac death (SCD) is a sudden unexpected death occurring quickly while otherwise having or showing no symptoms. The cause of death is often determined as a life-threatening arrhythmia. When such an event is not fatal, it is defined as sudden cardiac arrest (SCA). SCA and SCD are devastating and frightening and may occur without prior warning symptoms in seemingly healthy people.

Because of the gravity of these events, we decided to take a closer look into LCHADD cardiomyopathy by studying the medical records of adolescents and young adults who provided consent. Sixteen adolescents and young adults with a molecular diagnosis of LCHADD agreed to share their stories with us to understand the cardiac involvement associated with their diagnosis.

OUR CARDIAC FINDINGS

Five out of the 16 had infant cardiomyopathy (32%) where DCM was the most common. All resolved in early childhood without any complication. All sixteen participants were diagnosed before their first birthday. All had histories of hospitalizations due to metabolic decompensation with a concurrent illness as well as rhabdomyolysis crises throughout their lives. As they grew older, major cardiac involvement occurred in nine of 16 participants (57%), including SCD in 3, out-of-hospital SCA in 2, acute cardiac decompensations with heart failure and/or in-hospital cardiac arrest in another 2, end-stage dilated cardiomyopathy in one, and moderate restrictive cardiomyopathy in one other (Figure 1).

Five young adults had an out-of-hospital cardiac arrest or sudden death between 14 and 26 years of age (31%).

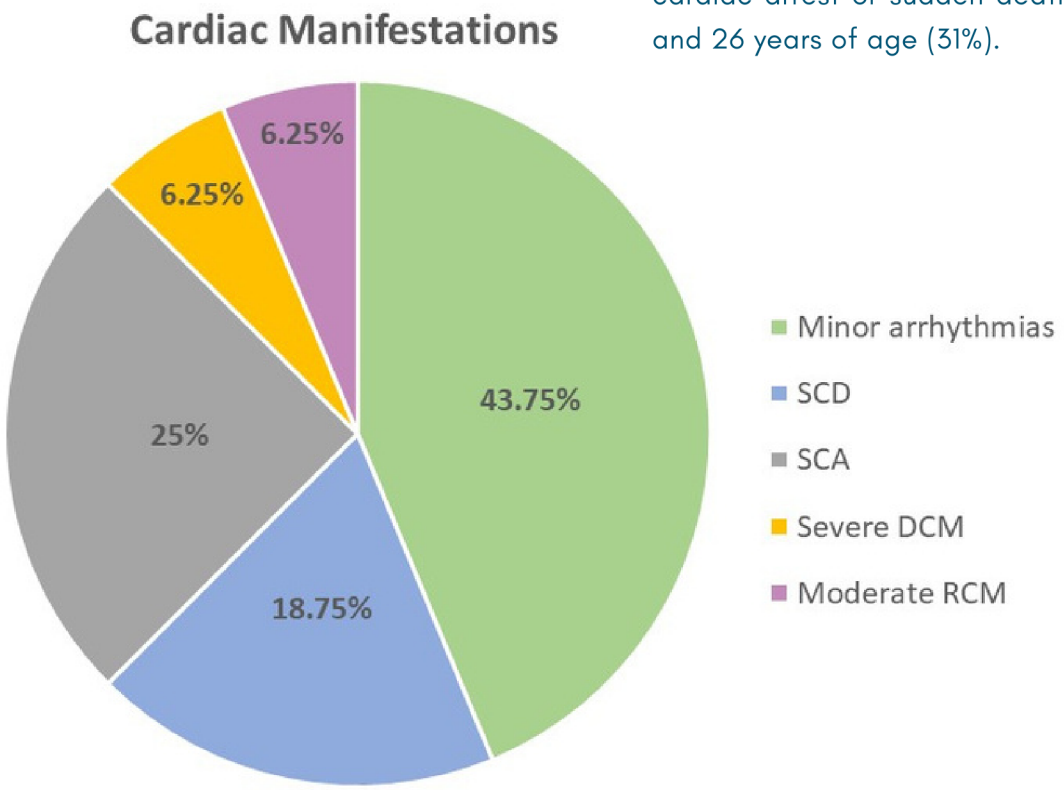


Figure 1. Percentage of our 16 subjects who experienced different cardiac manifestations.

Two of these had a witnessed sudden cardiac arrest. They were with their friends and were quickly rescued. They were apparently healthy before the event and were not experiencing a metabolic crisis at that time. They had minor CK elevation and had no kidney injury and after a hospitalization, they recovered completely. Two other teens and one young adult were found by their families in their homes with no signs of life. None had a history of being ill. There was no warning for these events. Two other young adults had life-threatening cardiac events while hospitalized for other reasons: one had severe rhabdomyolysis and kidney injury and had a cardiac arrest in this setting but was rescued; the other had an acute metabolic decompensation and sudden heart failure and while hospitalized had a cardiac arrest. After lengthy hospitalizations, they completely recovered. Another teen had progressive and ultimately fatal dilated cardiomyopathy. Mild cardiac dysfunction was noted at age 11 but despite repeated hospitalizations for heart failure and aggressive treatment from age 13 to 18, ultimately passed away at age 19. Lastly, another young adult has moderate restrictive cardiomyopathy with an enlarged atrium.

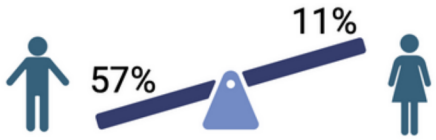
The other seven participants have milder cardiac manifestations. Several young adults have frequent PVCs. One teen had an increased frequency of these PVCs with loss of consciousness. Two have enlarged hearts (HCM) and the other two have minor abnormalities in the way the heart contracts and relaxes but are completely asymptomatic.

Twelve of the 16 young adults are alive and doing well (75%).

ASSOCIATIONS OF CARDIAC MANIFESTATIONS

SCA/SCD was more common in males than in females (57% vs 11%), was more common in those with a history of cardiomyopathy when they were an infant (60% vs 18%), and slightly more common in those who have two copies of the common LCHAD genetic variant G1528C compared to those with only one (33% vs 29%) (Figure 2). Systolic dysfunction was more frequent in males (71% vs 11%) and diastolic dysfunction was more frequent in females (45% vs 14%).

All five cases (4 male and 1 female) who had a history of resolved infant cardiomyopathy eventually developed a severe cardiac manifestation (SCA, SCD, or severe heart failure with in-hospital cardiac arrest) by their early 20s.



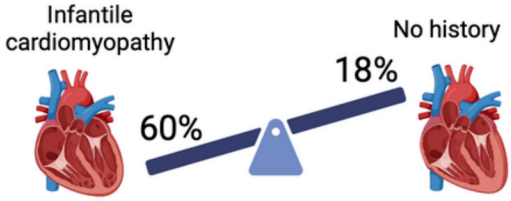


Figure 2. Association of SCA/SCD to participant sex and history of cardiomyopathy in infancy. SCA/SCD was more common in males and those with a history of cardiomyopathy in infancy.

WHAT SHOULD WE DO?

- **Know your story.** Every person is unique and LCHADD cardiomyopathy can be very different for each person, even among siblings. It is important to let your cardiologist know if you have a history of infantile cardiomyopathy, even if it is resolved.
- **Regular checkups with a pediatric cardiologist.** In this case series, 57% had cardiomyopathy of variable severity (dilated, hypertrophic, and restrictive), often mild at baseline but with the potential for acute worsening at times of metabolic crisis. Regular echocardiograms and Holter monitoring are necessary to monitor changes in cardiomyopathy and manage treatment. Your cardiologist may prescribe medication or decide if a loop recorder is necessary.
- **Take care of your diet.** Keeping a low-fat diet, MCT oil and/or C7 (aka triheptanoin, Dojolvi) is important. As well as moderate exercise with frequent breaks. Consistent self-care is important.
- **Implantable cardioverter defibrillator (ICD).** This is a small battery-powered device placed in the chest continuously checking the heartbeat. It detects and stops irregular life-threatening arrhythmias by delivering electric shocks when needed, to restore a regular heart rhythm. Since over 30% of these adolescents had a life-threatening arrhythmia *in the absence of acute metabolic decompensation or rhabdomyolysis crisis*, an ICD was considered necessary in five teens after their SCA. Three teenagers had it implanted after their SCA. In one teenager, the decision to implant an ICD was made because of an episode of non-sustained ventricular tachycardia and family history in a sibling, and in another teenager because of frequent PVCs and syncope. Our data suggests that males and those with a history of infant cardiomyopathy have a higher risk of SCA or SCD. In those cases, primary prevention with an ICD may be a good option following a thorough evaluation by a pediatric cardiologist.

There are limitations to our study and our knowledge about cardiac complications in LCHADD. Sixteen is a small number of patients and could be biased by those who volunteered to participate- those with heart complications may be more likely to volunteer. This is looking back at medical records which can be incomplete. We might have missed some important associations. We will continue to study cardiac complications of LCHADD gathering more information going forward.

Whether you have cardiac complications or you do not, if you would like to share your medical records and your story to help us learn more, you can join our FAOD repository. Visit the Clinical Trials Participation page on our website for more information: **https://www.ohsu.edu/school-of-medicine/gillingham-lab/clinical-research-participation**.