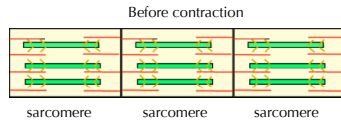


# The Sarcomere

Muscles are made up of muscle fibers. Within each muscle fiber, subunits of muscle (called sarcomeres) line up end to end in a long chain, as shown below. The mutations leading to HCM are all mutations in proteins found in the sarcomere.

## Myosin and Troponin

**Myosin** is the protein that makes up thick filaments (shown in green below). It is one of the major components of muscle. During contraction, myosin heads (gold) in the thick filaments (green) bind actin in the thin filaments (red) and pull the thin filaments in towards the center, thus shortening the sarcomere.



**Troponin** is a minor component of thin filaments. Troponin regulates contraction by preventing the myosin heads from binding actin, thus preventing contraction.

## Contraction in Action

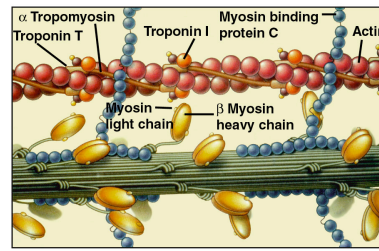


Image courtesy of Dr. Christine Seidman

Contraction occurs when:

- Calcium binds troponin
- Calcium binding causes troponin and tropomyosin to move
- Troponin and tropomyosin no longer block the myosin binding site on actin
- Myosin heads bind actin
- Myosin heads move and pull actin chain

# Mouse Models of Hypertrophic Cardiomyopathy

## Heart Structure and Function in Mutant Mice

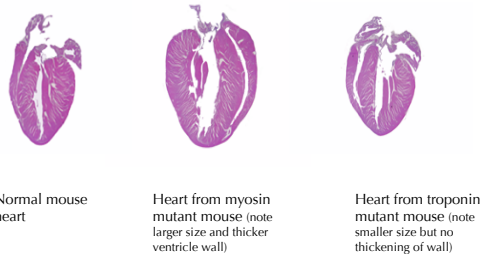
Dr. Leinwand's lab has generated mice with both myosin and troponin mutations. Mouse models allow researchers to better study the disease, and to design and test possible treatments. Below are mouse hearts from normal mice and mice with either a myosin or a troponin mutation.

### Structure

Notice that the heart is enlarged in mice with the myosin mutation and that the walls of the left ventricle are thicker.

In contrast, the heart from the mouse with a troponin mutation is smaller than normal size, and does not have thickened walls of the left ventricle. In humans, many people die suddenly with mutations in troponin, yet people with this form of the disease do not show symptoms prior to collapse.

**Studies of the troponin mutant mice may allow tests to determine early in life who is at risk for this form of HCM.**



Normal mouse heart

Heart from myosin mutant mouse (note larger size and thicker ventricle wall)

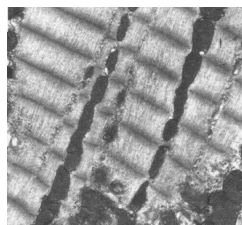
Heart from troponin mutant mouse (note smaller size but no thickening of wall)

### Function

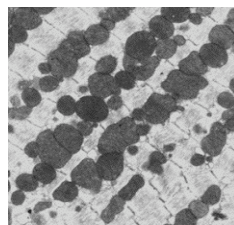
Myosin mutant mice show lower contraction and relaxation rates, while troponin mutant mice show significantly lower relaxation rates. These altered contraction/relaxation rates create abnormal pressures within the heart as well as decreased ability to pump blood throughout the body. This causes myosin mutant mice to be especially intolerant to stressful exercise.

## Cellular Structure in Mutant Mice

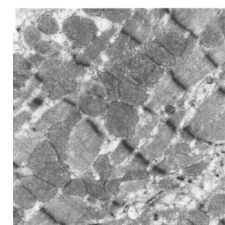
The cellular and sarcomere structure is different in heart tissue from mutant mice.



Normal Mouse  
Note organization and regular striation of muscle fibers



Myosin Mutant Mouse  
Note disarray in muscle fibers and disorganization of mitochondria.



Troponin Mutant Mouse  
Note disarray in muscle fibers and disorganization of mitochondria.