



Mutations and Disease
Mutations in the Myosin Gene
Teacher guide

General Information

- This is an advanced activity.
- It is designed to follow the activities on 3-dimensional protein structure, muscle contraction, and DNA sequencing, although you could choose to cover these materials differently.
- It assumes knowledge of DNA, 3-dimensional protein structure, mutations, amino acids, and translation. It would be a good activity for reviewing these concepts.
- This activity is based on the work of Dr. Christine Seidman that was published in the Journal of Clinical Investigation.

Nucleotide and Amino Acid Sequences

Family A. Unaffected

5' CTC TAC GGG GAC TTC CGG A 3'
Leu Tyr Gly Asp Phe Arg

Family A. Affected

5' CTC TAC GGG GAC TTC IGG A 3'
Leu Tyr Gly Asp Phe Trp

Family B. Unaffected

5' GTA CGG TIT CAG TTA CTT 3'
Val Arg Phe Gln Leu Ala

Family B. Affected

5' GTA CGG TGT CAG TTA CTT 3'
Val Arg Cys Gln Leu Ala

Question 1 – pg 3

Do both of these mutations lead to a change in amino acid sequence?

*Yes, in Family A, an arginine is replaced by a tryptophan
In Family B, a phenylalanine is replaced by a cysteine*

Questions 2 – 9 – pg 4

In Family A, what is the position number of the amino acid that is changed?

719

In Family A, what amino acid is usually found at this position?

Arginine (R)

In the affected member of Family A, what amino acid is found at this position?

Tryptophan (W)

How would a scientist name this mutation?

R719W

In Family B, what is the position number of the amino acid that is changed?

513

In Family B, what amino acid is usually found at this position?

Phenylalanine (F)

In the affected member of Family B, what amino acid is found at this position?

Cysteine (C)

How would a scientist name this mutation?

F513C

Question 10 – pg 6

What difference do you observe between the two curves? Which mutation has a bigger affect on survival?

The R719W mutation has a larger affect on survival. All people with this mutation have died by age 60, and many die much earlier. The F513C mutation has a far smaller affect on survival. Some people with this mutation have survived into their 80s.

Question 11 – pg 6

Look at the structure of the amino acids involved in the changes in the different families with hypertrophic cardiomyopathy. Do any of the changes involve a change in size, shape, polarity or charge?

The Phe513Cys mutation leads to a change in polarity and size but not in charge. The Arg719Trp mutation leads to a change in charge but not size.

Question 12 – pg 7

Look at the position of the amino acids involved in the changes in the different families with hypertrophic cardiomyopathy. Are any of the mutations in an area critical for the function of myosin?

The Phe513Cys mutation is not located in a protein or ATP binding site. The Arg719Trp mutation is located very near the actin binding sites.

Question 13 - pg 7

Using all the information you have so far – list at least two possible explanations for the difference between survival curves with the different mutations.

- 1. Mutations leading to a change in charge have the most profound affect on the function of myosin.*
- 2. Mutations located in or near the actin binding region have the most profound affect on the function of myosin.*

Question 14 - pg 9

How did the Arg719Trp mutation affect muscle contraction?

It was less affective

Questions 15 - 18, pgs 9 - 10

Why might the heart be larger in people with the Arg719Trp mutation (familial hypertrophic cardiomyopathy)?

*Heart will need to be larger since many of the myosin molecules don't work.
The heart tries to compensate by making itself larger*

How would muscle contraction have been affected if all the myosin molecules had the Arg719Trp mutation?

The muscle would not have contracted – myosin would not be able to bind actin

Why don't we find individuals with all of their myosin molecules affected?

They would die prior to birth since their heart would be unable to pump blood

Considering what you know about muscle contraction, could mutations in sarcomere proteins other than myosin result in problems similar to those seen with the Arg719Trp mutation? In what proteins might these mutations occur?

Mutations resulting in familial hypertrophic cardiomyopathy also occur in troponin, tropomyosin, and actin.