SNAPSHOT

ACTN3: Can genetics tell me if I am going to be an Olympic sprinter?

The Big Picture

- Can genetic technology be used to predict athletic performance or enhance the safety of athletes?
- What are the limits to using genetics in this way? What are some of the other factors to think about when we think about athletic talent?

As the genetic basis for certain health conditions is revealed, some doctors, coaches, and academic and athletic organizations are wondering whether genetic testing can provide health and safety benefits for athletes. Can genetics help minimize the risk of injury, or help a young person find the sport that is right for them? ACTN3 is a gene that encodes for the Alpha-actinin-3 protein. This protein is involved in contractions of skeletal muscles and is often referred to as the "speed gene" in the media. Could one gene be responsible for being a faster runner? How can we understand the contribution certain genes, or groups of genes, might have toward complex traits such as athleticism?

What are some of the genes that play a role in athletic performance?

Genetic testing kits can be purchased by parents, athletes, coaches, and athletic trainers. While these kits mostly focus on health and/or ancestry traits, some of these tests report on genetic markers that have been linked to athletic performance and risk for injuries. ACTN3 is the focus of this lesson, but let's have a look at a couple of other examples.

- The **ACE gene** (Angiotensin-Converting Enzyme) encodes a protein of the same name, which is involved in regulating blood flow throughout the body. Certain

variants of this gene have been linked to muscle efficiency as well as an increased production of certain muscle fibers.

- In 2020, all student athletes playing under NCAA rules are tested for a variant in the **Hemoglobin-Beta gene**, which can cause Sickle Cell Trait (SCT) as well as Sickle Cell Disease (SCD). Contrary to people living with SCD, most people living with SCT do not experience any serious health problems. However, when they engage in intense physical activities, medical complications can occur.
- **COL5A1 and COL5A2** are two genes that are involved in the production of specific collagen proteins, which are the main components of tendons and ligaments. Certain variants of these two genes have been shown to higher or lower the risk of common athletic injuries, such as ACL (anterior cruciate ligament) tears, which are often seen in the knees of soccer and basketball players.

What is ACTN3 and why is it of particular interest in athletics?

Humans have two broad categories of muscle fibers – fast twitch and slow twitch. Watch this two minute video to learn about the difference: "Sprinter vs. Marathoner".

The ACTN3 gene encodes for the Alpha-actinin-3 protein. This protein is found in fast-twitch muscle fibers, where it is involved with muscle contractions. This has led some to call ACTN3 "the sprinter gene". A specific variant in the DNA of the ACTN3 gene, called the 'X' variant, disrupts the production of functional Alpha-actinin-3 protein. If someone carries two copies of the X variant, meaning they inherited an X variant from each of their biological parents, then they do not have any functional Alpha-actinin-3 protein in their fast-twitch muscle fibers. Evidence shows that a lack of Alpha-actinin-3 effectively turns the fast-twitch muscle fibers into slow-twitch muscle fibers.

Can you predict whether you would be a great sprinter based on your ACTN3 variants? Around 20% of the general public carries two copies of the X variant, so they do not have functional Alpha-actinin-3 protein in their fast twitch muscle fibers. Among elite athletes that compete in sports where explosive strength involving fast-twitch muscle fibers is key, like sprinting, very few carry two copies of the X variant. It therefore appears that having two copies of the X variant makes it less likely that you will reach the top of the podium as a sprinter. Instead, these people may be more suited to compete in endurance sports.

Conversely, for those with functional Alpha-actinin-3 protein, can we assume they will be great sprinters? Since 20% of the general public carries two copies of the X variant, 80% of the general public has at least one copy of the functional ACTN3 gene and therefore have Alpha-actinin-3 protein in their fast twitch muscle fibers. However, 80% of the general public are clearly not elite sprinting athletes with Olympic gold medals! So, even though people with elite sprint/power performance are more likely to produce

functional Alpha-actinin-3 protein in their fast-twitch muscle fibers, there is clearly a lot more to being an elite athlete than the simple presence of a functional ACTN3 gene.

Genetic testing in sports: Scientific and social considerations

Biology is complex. A trait such as athleticism is influenced by hundreds of genes – ACTN3 is just one of many. In addition, the exact role of each of these many genes and how they interact with each other to influence a person's athleticism is extremely complex and beyond our current understanding. On top of this, a person's environment and lifestyle are also major contributors to their athletic capabilities.

Take ice hockey as an example. A hockey player's success is impacted by a number of traits, including strength, muscle mass, muscle fiber composition, lung capacity and susceptibility to injury. Many of these traits are influenced by genetics, and research has begun to uncover some of the genes that are involved. These traits and success overall are also impacted by environmental and lifestyle factors – including training, nutrition, access to equipment, and the cultural value assigned to certain athletic endeavors. For example, why do many ice hockey players come from Western Canada and not Hawaii? A person's physical attributes are part of the puzzle, but access to hockey rinks, youth development programs, and a culture where hockey is revered are part of the equation as well.

No single genetic variant can account for athletic success - this includes the idea that a single "speed gene" exists. Numerous genes have been linked to traits related to athletic performance, with more discoveries being made all the time. Genes are one part of an intricate puzzle that also includes environmental factors, such as nutrition, training and cultural pressures. And all of these factors interact with each other in a variety of ways, forming a complex picture. A genetic test that reveals what variant of the ACTN3 gene a person carries, is not very predictive of whether they will be a gold medalist at the Olympics.

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STUDENT WORKSHEET

What have we learned? A few short questions:

1. List the names of two genes mentioned in this lesson (that are not ACTN3) and describe their possible links to athletic performance.

2. In what type of muscle-fibers is the Alpha-actinin-3 protein found? Explain the role of these muscle fibers in skeletal muscles.

3. Are ACTN3 variants predictive of who will be an Olympic-level sprinter and who will not be? Why or why not?

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TEACHER'S GUIDE

Below you will find resources to give a more in-depth explanation of the ACTN3 gene, its assorted alleles, and its role in muscle contraction. You will also find an answer guide for the student quiz/assessment.

If you have the time, students may appreciate watching David Epstein's Ted Talk, author of *The Sports Gene*, "Are athletes really getting faster, better, stronger?" from March 2014. It puts this discussion about genetics and athletics in to a more broad context and explains how multi-faceted athletic performance can be.

Science Explainer: ACTN3 (alpha-actinin-3)

The ACTN3 gene plays a role in fast twitch muscle fibers, responsible for generating powerful muscle contractions. There are two versions of the ACTN3 gene that are commonly found in people, R and X. The R variant can produce the actinin-3 protein, while the X variant does not. The R variant of ACTN3 has been linked to sprinting ability in studies showing that, whereas around 20% of the general public carry 2 copies of the X variant, this is rarely the case in elite sprinters. A genetic test for ACTN, however, cannot predict which individuals will become elite sprinters; it is unusual for an elite sprinter not to have the R variant, but there are exceptions.

Gene function

The ACTN3 gene encodes the Alpha-actinin-3 protein that is expressed specifically in fast twitch muscle fibers. The Alpha-actinin-3 protein binds to a component of the cytoskeleton, known as actin, that is involved in muscle contractions.

Nature of ACTN3 variants

The R and X variants of the ACTN3 gene differ at a single nucleotide (known as a *single nucleotide polymorphism* or SNP) in the DNA sequence, where a C (cytosine) is changed to a T (Thymine). The R variant encodes the amino acid, arginine (R), at position 577 in the protein. The X variant encodes a stop codon that prematurely signals the ribosome to stop translation (also referred to as a *nonsense* SNP). As a result, individuals *homozygous* for the X variant (X/X) do not produce functional actinin-3 protein.

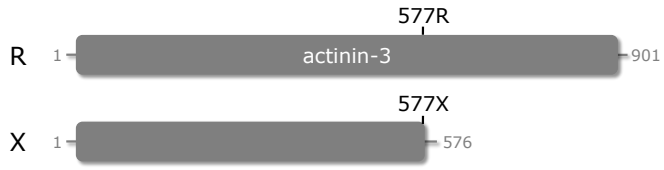

Diagram of the actinin-3 protein encoded by the R and X variants. The X variant produces a short, non-functional protein.

Answer Key

1. List the names of two genes mentioned in this lesson (that are not ACTN3) and describe their possible links to athletic performance.

    - The ACE gene encodes a protein that is involved in regulating blood flow throughout the body, and is linked to muscle efficiency and the production of certain muscle fibers.
    - Hemoglobin-Beta gene, of which certain variants can cause Sickle Cell Trait (SCT) and Sickle Cell Disease (SCD). Contrary to people living with SCD, most people living with SCT do not experience any serious health problems. However, when they engage in intense physical activities, medical complications can occur.
    - COL5A1 and COL5A2 are involved in the production of specific collagen proteins, which are the main components of tendons and ligaments. Having certain variants can raise or lower the risk of injures like ACL tears.

2. In what type of muscle-fibers is the Alpha-actinin-3 protein found? Explain the role of these muscle fibers in skeletal muscles.

Alpha-actinin-3 protein is found in fast-twitch muscle fibers. These muscle fibers fire rapidly and provide short bursts of power, which are best for explosive body movements in sports like sprinting or ice hockey.

3. Are ACTN3 variants predictive of who will be an Olympic-level sprinter and who will not be? Why or why not?

Student answers should include an understanding of the key concepts that while it is rare for an elite-level power athlete, such as a sprinter, to have two copies of the X variant of the ACTN3 gene, it can happen in rare cases.

Conversely, the presence of a functional copy of the ACTN3 (as is the case for 80% of the general public) does not make someone an Olympic sprinter. No single genetic variant can account for athletic success. Numerous genes have been linked to athletic performance, as well as environmental factors, such as nutrition, training and cultural pressures. A genetic test that reveals what variant of the ACTN3 gene a person carries, is thus not very predictive of whether they will be a gold medalist at the Olympics.