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Can specific genes cause muscles to grow faster or stronger, and can genetic tampering give athletes an unnatural edge?

By Larry Greenemeier | July 31, 2012

Take a close look at the athletes competing in this year's Summer Olympic Games in London—their musculature will tell you a lot about how they achieved their elite status. Endless hours of training and commitment to their sport played a big role in building the bodies that got them to the world's premier athletic competition. Take an even closer look—this one requires microscopy—and you'll see something else, something embedded in the genetic blueprints of these young men and women that's just as important to their success.

In nearly all cases, these athletes have realized the full potential laid out by those genes. And that potential may be much greater to begin with than it was for the rest of us mortals. For instance, the genes in the cells that make up sprinter Tyson Gay's legs were encoded with special instructions to build up lots of fast-fiber muscles, giving his legs explosive power out of the starting blocks. In comparison, the maximum contraction velocity of marathoner Shalane Flanagan's leg muscles, as dictated by her genes, is much slower than Gay's yet optimized for the endurance required to run for hours at a time with little tiring. Such **genetic fine-tuning also helps competitors in basketball, volleyball and synchronized swimming**, although the impact might be much less because effective teamwork and officiating also influence success in those sports.

When the gun goes off for the 100-meter sprint, when swimmers Michael Phelps and Ian Thorpe hit the water, when Tom Daley leaps from his diving platform, we will be seeing the finest that the world's gene pool has to offer, even though scientists are still trying to figure out which genes those are. Unfortunately, history dictates that we may also see the finest in gene manipulation, as some athletes push for peak performance with the help of illegal substances that are becoming increasingly difficult to detect.

The skinny on muscles

The human body produces two types of skeletal muscle fibers—slow-twitch (type 1) and fast-twitch (type 2). The fast-twitch fibers contract many times faster and with more force than the slow-twitch ones do, but they also fatigue more quickly. Each of these muscle types can be further broken down into subcategories, depending on contractile speed, force and fatigue resistance. Type 2B fast-twitch fibers, for example, have a faster contraction time than type 2A.

Muscles can be converted from one subcategory to another but cannot be converted from one type to another. This means that endurance training can give type 2B muscle some of the fatigue-resistant characteristics of type 2A muscle and that weight training can give type 2A muscle some of strength characteristics of type 2B muscle. Endurance training, however, will not convert type 2 muscle to type 1 nor will strength training convert slow-twitch muscle to fast. Endurance athletes have a greater proportion of slow-twitch fibers, whereas sprinters and jumpers have more of the fast-twitch variety.

Just as we can alter our muscle mix only to a certain degree, muscle growth is also carefully regulated in the body. One difference between muscle composition and size, however, is that the latter can more easily be manipulated. Insulinlike growth factor 1 (IGF-1) is both a gene and the protein it expresses that plays an important role during childhood growth and stimulates anabolic effects—such as muscle building—when those children become adults. *IGF-1* controls muscle growth with help from the *myostatin (MSTN)* gene, which produces the myostatin protein.

More than a decade ago H. Lee Sweeney, a molecular physiologist at the University of Pennsylvania, led a team of researchers who used genetic manipulation to create the muscle-bound "Schwarzenegger mice". Mice injected with an extra copy of the *IGF-1* gene added muscle and became as much as 30 percent stronger. Sweeney concluded that it is very likely that differences in a person's IGF-1 and MSTN protein levels determine his or her ability to put on muscle when exercising, although he admits this scenario has not been studied widely.

Slow-fiber muscle growth and endurance can likewise be controlled through gene manipulation. In August 2004 a team of researchers that included the Salk Institute for Biological Study's Ronald Evans reported that they altered a gene called *PPAR-Delta* to enhance its activity in mice, helping nurture fatigue-resistant slow-twitch muscles. These so-called "marathon mice" could run twice as far and for nearly twice as long as their unmodified counterparts.

This demonstrated ability to tinker with either fast- or slow-twitch muscle types begs the question: What would happen if one were to introduce genes for building both fast- and slow-twitch muscle in an athlete? "We've talked about doing it **but have never done it**," Sweeney says. "I assume you'd end up with a compromise that would be well suited to a sport like cycling, where you need a combination of endurance and power." Still, Sweeney adds, there has been little scientific reason (which translates into funding) to

conduct such a study in mice, much less humans.Gene manipulation will have its most significant impact in treating diseases and promoting health rather than enhancing athletic abilities, although sports will certainly benefit from this research. Scientists are already studying whether gene therapies can help people suffering from muscle diseases such as muscular dystrophy. "A lot has been learned about how we can make muscles stronger and bigger and contract with greater force," says Theodore Friedmann, a geneticist at the University of California, San Diego, and head of a gene-doping advisory panel for the World Anti-Doping Agency (WADA). Scientific studies have introduced IGF-1 protein to mouse tissue to prevent the normal muscle degradation during aging. "Somewhere down the road efforts could be made to accomplish the same in people," he adds. "Who would not stand in line for something like this?"

Gene therapy has already proved useful in studies unrelated to muscle treatment. In December 2011, for example, a team of British researchers reported in *The New England Journal of Medicine* that they were able to treat six patients with hemophilia B—a disease in which blood cannot clot properly to control bleeding—by using a virus to deliver a gene enabling them to produce more of the clotting agent, factor IX.

Hard targets

Despite experiments with IGF-1 and MSTN protein levels in mouse muscle, identifying which genes are directly responsible for athletic prowess is a complicated matter. "What we've learned over the past 10 years since the sequencing of the human genome is that there's a heck of a lot more complexity here than we first envisioned," says Stephen Roth, a University of Maryland associate professor of exercise physiology, aging and genetics. "Everybody wants to know what are the genes that are contributing to athletic performance broadly or muscular strength or aerobic capacity or something like that. We still don't have any hard targets solidly recognized by the scientific community for their contribution to athletic performance."

By 2004 scientists had discovered more than 90 genes or chromosomal locations they thought were most responsible for determining athletic performance. Today the tally has risen to 220 genes.

Even with this lack of certainty, some companies have already tried to exploit what has been learned so far to market genetic tests they claim can reveal a child's athletic predispositions. Such companies "are sort of cherry-picking some literature and saying, 'Oh, these four or five gene variations are going to tell you something,'" Roth explains. But the bottom line is the more studies we've done, the less certain we are that any of these genes are really strong contributors by themselves."

Atlas Sports Genetics, LLC, in Boulder, Colo., began selling a $149 test in December 2008 the company said could screen for variants of the gene *ACTN3*, which in elite athletes is associated with the presence of the protein alpha-actinin-3 that helps the body produce fast-twitch muscle fibers. Muscle in lab mice that lacks alpha-actinin-3 acts more like slow-twitch muscle fiber and uses energy more efficiently, a condition better suited to endurance than mass and power. "The difficulty is that more advanced studies have not

found exactly how loss of alpha-actinin-3 affects muscle function in humans," Roth says.

ACE, another gene studied in relation to physical endurance, has rendered uncertain results. Researchers originally argued that people with one variant of *ACE* would be better at endurance sports and those with a different variant would be better suited to strength and power, but the findings have been inconclusive. So although *ACE* and *ACTN3* are the most recognized genes when it comes to athletics, neither is clearly predictive of performance. The predominant idea 10 or 15 years ago that there might be two, three or four really strong contributing genes to a particular trait like muscular strength "is kind of falling apart," Roth says. "We've been realizing, and it's just been borne out over the past several years, that it's not on the order of 10 or 20 genes but rather hundreds of genes, each with really small variations and huge numbers of possible combinations of those many, many genes that can result in a predisposition for excellence.

"Nothing about the science changed," he adds. "We made a guess early on that turned out not to be right in most instances—that's science."

Gene doping

WADA turned to Friedmann for help after the 2000 Sydney Summer Olympics after rumors started flying that some of the athletes there had been genetically modified. **Nothing was found**, but the threat seemed real. *Officials were well aware of a recent gene therapy trial at the University of Pennsylvania that had resulted in the death of a patient."In medicine, such risks are accepted by patients and by the profession that danger is being undertaken for purposes of healing and preventing pain and suffering,"* Friedmann says. **"If those same tools when applied to a healthy young athlete were to go wrong, there would be far less ethical comfort for having done it.** And one would not like to be in the middle of a society that blindly accepts throwing [*erythropoietin (EPO)*] genes into athletes so they can have improved endurance performance." *EPO* has been a favorite target for people interested in manipulating blood production in patients with cancer or chronic kidney disease. It has also been used and abused by professional cyclists and other athletes looking to improve their endurance.

Another scheme has been to inject an athlete's muscles with a gene that suppresses myostatin, a protein that inhibits muscle growth. With that, Sweeney says, "you're off and running as a gene doper. I don't know if anyone is doing it, but I think if someone with scientific training read the literature they might be able to figure out how to succeed at this point," even though testing of myostatin inhibitors injected directly into specific muscles has not progressed beyond animals.

Myostatin inhibitors as well as *EPO* and *IGF-1* genes have been early candidates for gene-based doping, but they're **not the only ones**, Friedmann says. The *vascular endothelial growth factor (VEGF)* gene instructs the body to form signal proteins that help it increase blood flow by sprouting new blood vessels in muscle. These proteins have been used to treat macular degeneration and to restore the oxygen supply to tissues when blood circulation is inadequate. Other tempting genes could be those that affect

pain perception, regulate glucose levels, influence skeletal muscle adaptation to exercise and aid respiration.

Games at the 2012 Olympics

Gene manipulation is a big wild card at this year's Olympics, Roth says. "People have been predicting for the past several Olympics that there will be gene doping at the next Olympics, but there's never been solid evidence." Gene therapy is often studied in a medical context, and it fails a lot of the time, he notes. "Even if a gene therapy is known to be solid in terms of treating a disease, when you throw it into the context of athletic performance, you're dealing with the unknown."

The presence of gene doping is hard to detect with certainty. Most of the tests that might succeed require tissue samples from athletes under suspicion. **"We're talking about a muscle biopsy, and there aren't a lot of athletes who will be willing to give tissue samples when they're getting ready to compete,"** Roth says. Gene manipulation is not likely to show up in the blood stream, urine or saliva, so the relatively nonintrusive tests of those fluids are not likely to determine much.

In response, WADA has adopted a new testing approach called the Athlete Biological Passport (ABP), which will be used at the London Olympics. Several international sporting authorities such as the International Cycling Union have also begun to use it. The key to ABP's success is that, rather than looking ad hoc for a specific agent—such as *EPO*—the program monitors an athlete's body over time for sudden changes, such as a jump up in red blood cell count.

Another way to detect the presence of gene doping is to recognize how the body responds to a foreign gene—notably, defense mechanisms it might deploy. "The effect of any drug or foreign gene will be complicated by an organism trying to prevent harm from that manipulation," Friedmann says—rather than from intended changes induced by *EPO*, for example.

The Olympic games make clear that all athletes are not created equal, but that hard work and dedication can give an athlete at least an outside chance of victory even if competitors come from the deeper end of the gene pool. "Elite performance is necessarily a combination of genetically based talent and training that exploits those gifts," Roth says. "If you could equalize all environmental factors, then the person with some physical or mental edge would win the competition. Fortunately those environmental factors do come into play, which gives sport the uncertainty and magic that spectators crave."