In 1998 Hugh Montgomery and his fellow scientists discovered the first “fitness gene.” Now that number is up to nearly 200 such genes. The World Anti-Doping Agency (WADA) recognizes that the rapid advances in human gene therapy may provide serious prospects for using genes, genetic elements, and cells that have the capacity to enhance sports performance. So there appears to be a definite link between genetics and sport and doping. Still, WADA considers most genetic manipulations illegal. However, not all uses of genetic information should be considered illegal, as there may be legitimate, and legal, ways to implement genetics in sport that may soon be of benefit to you. Read on...

**NEW GENES**
Steroids may be the performance-enhancing drugs of the past

Original Research

A THREE-TIME OLYMPIC GOLD MEDALIST AND TWO-TIME WORLD CHAMPION IN NORDIC SKIING, EERO MÄNTYRANTA HAS A GENETIC “DEFECT” THAT BRINGS MORE OXYGEN TO HIS MUSCLES. COULD GENETIC DOPING MIMIC THIS EFFECT?

PHOTO: SPORTS MUSEUM FINLAND

**Power Key:** gene doping, ergogenic aids, performance enhancement
NEED POWER?

Here are some interesting facts from the Human Genome Project:

- Humans have 23 chromosomes and about 25,000 genes.
- Chimps have 24 pairs of chromosomes, and 13 are identical to ours.
- Humans seem to share about 96% of a chimp’s genes.
- Chimps share about 97% of a gorilla’s genes.
- Humans share about 30% of their genes with a banana.
- About 97% of a human’s genes are considered junk as only about 3% of them are coded for functional proteins or cellular instructions.

Genetics essentially refers to how traits are inherited in genes and associated DNA sequences. DNA (deoxyribonucleic acid), a type of nucleic acid principally found in the nuclei and mitochondria of animal and plant cells, is considered the autoreproducing component of chromosomes and the repository of hereditary characteristics. Epigenetics, on the other hand, relates to changes in gene function that cannot be explained by changes in DNA sequence. The difference between genetics and epigenetics is that, in epigenetics, the DNA sequence itself is not changed. Changes in gene function occur that cannot be explained by changes in DNA sequence; rather, they occur due to external influences. Enter your muscle cells. If you were to change the internal milieu of your muscle fibers, you could experience a positive epigenetic response. Of course you might not, which might explain why some training programs work better than others and why some athletes may make better training gains than others.

There is a family of genes called apolipoprotein or APO for short. These genes, simply referred to as APO-A, -B, -C, and -E, are spread over various chromosomes (a body within a cell nucleus that bears genes). Now, APO-E is a polymorphic gene because it has variants E2, E3, and E4. E4 is not a “good” gene as it is associated with coronary heart disease. APO-E4 is also relevant to sport. Boxers with two E4 genes, for example, seem to be at higher risk of early Alzheimer’s or Parkinson’s disease by age 50.

Doped Up on Genes

In 2004 WADA defined gene doping as “the non-therapeutic use of genes, genetic elements and/or cells, which have the capacity to enhance athletic performance.” Here are some possibilities:

- There is an ACE gene that can enhance control of cellular chemical processes, especially protein synthesis and insert them into the cell’s genome. So a gene therapist can delete a harmful gene and perhaps correct it. This was done about 15 years ago by removing lymphocyte stem cells from a young patient suffering from severe combined immune deficiency (SCID), infecting them with a retrovirus that contained the correct information, and re-injecting the lymphocytes into her body. Her lymphocyte count tripled, her antibody levels rose, and she made 25% of the normal amount of necessary proteins to combat the disease. Could this sort of gene therapy be helpful to those suffering, for example, from Marfan’s syndrome, a cause of sudden death in tall athletes playing basketball and volleyball?
endurance performance by possibly diverting some ATP away from “wasted” heat generation and using it primarily for furnishing energy for endurance activities. The AAV gene can “infect” muscle in a harmless way and function as a vector for gene coding for insulin-like growth factor I (IGF-1), which triggers the replication of muscle satellite cells, which in turn causes muscle growth. In rats, using this gene doubled their strength, and even sedentary rats improved their strength by 15%.

Myostatin is a gene that inhibits muscle growth. As an example, if you slice off a bunch of muscle in an accident, your body would have to know when to stop healing and growing the muscle back; this is the role of myostatin. By turning this gene partially off, which is much more difficult to do than turning on a gene, scientists have been able to produce larger beef breeds and make racing whippets bigger. Of course, the added muscle in these dogs can end up being a negative, since they then have to move more weight, so in the end the procedure did not make them faster than the untreated dogs. In mice, the process not only produced unusually muscular mice, but also caused an effect called hyperplasia: muscle cells actually split so that instead of having one, a mouse would end up with two.

In the early 1960s, triple-Olympic Nordic skiing champion Eero Mäntyranta was shown to have a favorably mutated gene called an EPO-receptor gene that increased his hemoglobin concentration, thus carrying more oxygen to the muscle. By injecting an EPO gene into mice and primates, just once, hematocrit (the percentage of the volume of a blood sample that is occupied by cells) levels rose from 50% and 40%, respectively, to over 70% for a duration of four to six months. And vascular endothelial growth factor has been shown to increase vascular supply in elderly humans by growing new blood vessels. In regard to muscle strength and power, signal transduction pathways are responsible for either increasing or decreasing the function of genes, such as controlling fast and slow muscle function. By manipulating this function, the fast-twitch muscle fibers could be turned on more while lowering the contribution of the slow-twitch muscles, thereby enhancing performance in sports requiring a great deal of strength and power.

On the surface, the above procedures might sound appealing. However, there are major risks involved. Remember the patient treated successfully for SCID? As that research continued, two of 13 patients developed cancer as a result of this treatment. In primates, severe autoimmune reactions occurred as a result of EPO gene insertions, and a human patient treated genetically for an inborn error of metabolism died when the treated cells were turned on too much, leading to multiple organ failure. As for myostatin, you might be thinking that there could not possibly be anything wrong with muscles that are too big. Perhaps this holds true if you are a bodybuilder, but research presented in 2007 in the Proceedings of the National Academy of Sciences of the United States of America found that mice treated with a myostatin gene inhibitor grew bigger muscles than their normal counterparts, yet those muscles were not able to demonstrate any more strength than the muscles of the untreated mice. Clearly, bigger is not necessarily better, especially if your muscle has to be functional.

Gened Up

So what does the future hold in regard to gene doping? Perhaps that question is already moot. In 2001 Peter Schjerling of the Copenhagen Muscle Research Center indicated that gene doping is basically impossible to detect. This is because cell
signaling, or cell signaling products, are indistinguishable from natural events. In 2002 Alan Kingsman of Oxford Medica announced the launch of its product Repoxycogen. This product allows mice to switch on a gene in response to low oxygen levels, thus providing more oxygen when needed, such as during exercise. And Theodore Friedman of WADA stated that gene doping could occur in the 2008 Olympics in Beijing, an event that is now history. In the end, and only speaking for this particular time in history, the limiting factor is the gene promoter, that which facilitates the transfer of genetic information. There is a marked lack of information about the promoters for most human genes, which makes using gene therapy as an ergogenic for sport less than practical.

GET POWER!

It seems rather clear that gene doping in sport should be illegal. Fundamentally, how is taking a genetic compound that turns on fast-twitch muscle production any different from taking an illegal anabolic androgenic steroid (AAS) to increase muscle size and strength? And that is why gene doping is illegal in sport. Unfortunately, we lack the ability to detect gene doping—for now. But there is also another issue to be considered—the question of safety. Is running 100 meters in five seconds really worth your life? And what about the non-competitive fitness enthusiasts, the people that a previous research review in JOPP identified as the largest group of AAS users? It seems incredibly silly to us for someone to take AAS in order to bench 350 or have a 17-inch arm. But this would probably be the same group of people who would fall victim to unscrupulous medico-scientific sports gurus who would bypass the normal safety tests for genetic procedures and expose these recreational athletes, and of course competitive athletes, too, to immense risks. Perhaps the study author puts it best: “The possibilities for gene therapy are excitingly promising, but the possibilities for gene doping are worryingly impending. Both are fraught with risks and with difficulties; far more so perhaps in doping than in therapy, as the latter will tackle specifically defined genetic errors.”

But perhaps it is not all doomsday when talking about gene therapy and sport. A recently coined phrase, athleticogenomics, describes the integration of genome data sets with physiological performance. It is not only the encoded protein itself, but its rate of transcription, that is important. That means that gene-expression profiling could be used in sports competition. Just as you might respond to different sorts of headache medication differently, allowing your physician to dial in the proper medicine, so your coach could use your unique transcription rates in an effort to have you train in the most ideal way. You can see that this process does not amount to gene doping—it is rather gene profiling and utilization. And of course this could also be used to identify talent. After all, even though you really enjoy weightlifting, it is quite possible that you would be a much better powerlifter. There would be nothing illegal about looking at your genes to find out for sure.

REFERENCES

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