Genetics & Sports

The Genes who make the Champions: "Can Genes predict Athletic Performance?"

Dr. Karl J. Neeser*

There is scientific evidence that about 200 genes have some positive association with fitness-related performance, but today's research is just scratching the surface and there are only a few convincing of the genes studied so far and consistently associated with sports-related performances.

Genes and Sport – Introduction

Heritability plays an important role in human performance. Researchers estimate that performance related traits important to elite athletes have heritability values of about 50% for maximal oxygen uptake (VO2max), 42-46% for cardiac output, 40-50% for muscle fibre type proportions, and 67% for explosive muscle power (Macarthur et. al, 2004). Thus it is probably favourable to posses the right blend of genes that are conducive to an athlete's specific discipline, especially for muscular strength and endurance.

Today, athletes and coaches are curious about the possible role of genetics in determining who will be a champion. Coaches would like to know if an athlete's genetic background could be used to help select those who have a better chance of succeeding. Athletes wonder if the genes they have inherited might help or limit their abilities to perform at high levels in various sports. I hope that my today's presentation will address these issues.

---

* Visiting Professor, School of Sports Science, Chulalongkorn University.

Basic Concepts

Genes are parts of the DNA molecules in every cell of the body that carry information responsible for the subsequent *production of specific chains of amino acids,* which are then used to develop specific proteins. The **genotype** is the total combination of the thousands of genes within the body, that is, the genetic potential of a person.

However, not all of the genes are used or expressed to their full potential. The anatomical, biochemical, physiological, and behavioural characteristics of a person at any given time represent the extent to which the various genes are expressed: These characteristics are known as **phenotypes**. Examples of phenotypes include blond hair, green eyes, a resting heart rate of 60 beats per minute, a maximal oxygen intake (VO2max) of 50ml/kg/min or a body weight of 75 kg.

Genes affect how a phenotype is expressed now, as well as how it will respond to a change in environment (Bouchard et al., 1999). While one's eye colour is set for life, one might reduce blood pressure with regular physical activity, increase VO2max with training, and lose weight by dieting. The speed and the extent to which changes in phenotypes occur are affected by our genetic background. And this is now important: For a particular phenotype there are people who are superior responders, average responders, poor responders, and non-responders to a change in the environment. Thus, there are people who lose weight or who improve their fitness and athletic performance more easily than others.

It is this variation in phenotypes and how they respond to changes in the environment that allows scientists to study the role of genes. For instance, if all participants in a study improve their VO2max by 15% after 12 weeks of standardized exercise training, then it is clear, that genes play a minor role and it is only the change in the environment (in this case, training) that is important. On the other hand, if there is a large variation in adaptations to the same training program, genes may be important.

Today, in medicine, many studies are on the way with families with biological and adopted children, as well as with identical twins (where the genetic background is the same) to see the influence of genes on various phenotypes when the environment is similar. And as a consequence,

genetic diagnostics is becoming more and more common in practical medicine, because small changes in the DNA, so called SNIPS, Single Nucleotide Polymorphisms, are important for our health. Through the knowledge of our genetic polymorphism we can gain control over our health care. We can practice individualized preventive medicine. The diagnostic of polymorphism will strongly influence health care in the next 10 years, it has already reached an important place in preventive medicine and will keep this place in the future.

What effect does genetics play in champion athletes?

Genes determine our potential for developing many of the structural and functional characteristics important in determining sports performance (Bouchard et al., 1995, Rankinen et al., 2004). For instance, to be a successful centre in Basketball, you must inherit the gene for tall stature. For other characteristics, though, diet training, and other environmental factors play a huge role in how your genetic potential is expressed. For example, you may have the genetic potential for a low body weight, but eating too much and exercising too little can overcome that genetic message and cause you to become obese.

The chart illustrates how strongly the genes typically affect some of the structural, functional, and performance characteristics of the body. Those characteristics in the chart for which genes have only a low to moderate effect (f. ex. balance, reaction time, accuracy of movements) are likely to be more powerfully influenced by training, diet, and other environmental factors than are characteristics like strength, flexibility and endurance, for which the genes have a large effect as we will see.

Example of Effects of Genes on Structure, Function, and Performance

TABLE 1. Effects Of Genes On Structure, Function, And Performance

CHARACTERISTIC	EFFECT OFGENES
Height, Length of Arms	Large
Waist Girth	Small to Moderate
Muscle Size	Large
Muscle Fiber Composition (Fast- and Slow-Twitch)	Large
Mitochondria/Gram of Muscle	Small
Heart Size	Large
Lung Size And Volume	Large
Activities of Muscle Enzymes Used to Produce Energy	Small to Moderate
Resting Heart Rate	Large
Blood Pressure	Moderate
Air Flow in Lungs	Moderate
Muscular Strength	Large
Muscular Endurance (e.g., pushups, pull-ups)	Moderate to Large
Movement Speed	Moderate
Balance	Small
Flexibility of Joints	Large
Reaction Time	Small to Moderate
Accuracy of Movements	Small to Moderate
Aerobic Endurance (e.g., distance running or cycling)	Moderate to Large
Anaerobic Power (maximal cycling power output in 10 seconds)	Moderate

Table 1

There are many phenotypes for which the effects of the genes have been determined. (Table 1; Bouchard et al., 1997). Genes have a large effect on height, length of arms and legs, even length of trunk. Genes have a large influence on muscle seize and composition (percentage of fast-twitch and slow-twitch fibres). Because muscle strength is closely related to fibre composition, genes have a very large effect on strength, too.

On the other hand, the activities of muscle enzymes, important in energy metabolism and the number of mitochondria within a given amount of muscle tend to be less influenced by genes because they can be modified by different types and amounts of physical activity. To summarize, the effect of the genes in muscles is great relative to structure (contractile proteins and size) but not necessarily to function. In the case of the phenotype “muscular endurance”, which is affected by both structural and functional factors, the genetic effect is “only” moderate to large.

Similarly, size of the lungs and volume is affected greatly by the genes, but such functional measures as rates of airflow are not. In the cardiovascular system, there are large genetic effects on

the size of the heart, as well as the size and the structure of the coronary arteries. Blood pressure tends to be less affected by genes because it can be modified by body weight and diet for example.

Relative to exercise, genes have a large effect on VO2max, maximal heart rate, and maximal lung ventilation (example cyclists). Evidence suggests that cardiovascular endurance (e.g., the total amount of work that one can perform in 90 min.) is even more strongly affected by genes than is VO2max. This is probably because many physiological and biochemical variables are involved in endurance exercise, and genes can affect each of them (Bouchard et al., 1999).

Characteristics for which the genes have only a low moderate effect, balance, reaction time, accuracy of movements are likely to be more powerfully influenced by training, diet, and other environmental factors than are characteristics like strength and flexibility, for which the genes have a large effect.

Genetics and Training

The genes also determine the speed and extent to which our body's performance characteristics respond to exercise training, diet, and other environmental factors (Bouchard et al., 1997).

TABLE 2. Effects Of The Genes On Responses To Exercise Training

RESPONSE TO TRAINING	EFFECT OFGENES ON RESPONSE
Strength	Small
10-Second Maximal Power Output—Bicycle Ergometer	Small
90-Second Maximal Power Output—Bicycle Ergometer	Large
Aerobic Endurance	Moderate to Large

Table 2

Let me give you an example: for a given characteristic, such as aerobic endurance or muscular strength, some people are strong responders to training (>large), others are moderate or weak (>small) responders to the same training. What it means for instance, is that even though your genetic potential for distance running may be less impressive than that of a competitor, you may be able to develop that potential more quickly and completely by training hard so that you can always beat your opponent. Until today there is still insufficient published research on how strongly genes

affect an individual's response to training, but Table 2 lists some of early conclusions from this research. But new studies now already have shown at least moderate genetic effect on the response of strength to resistance training for example. The training effect on power output in 10 seconds is probably only weakly affected by the genes, possibly because technique and reaction time – both little affected by genes – are more important than raw strength, more strongly affected by genes.

Tactics and techniques – such as drafting and using an aerodynamic posture in cycling – are critical to success in many sports but are not affected by the genes. Champions at the elite level must be experts at tactics and technique in addition to possessing the necessary genetically determined attributes for success in their sports. But in fact, the problem is much more complex. Depending on the sport, many systems in the body are involved, for example in distance running: cardiovascular, respiratory, neuromuscular, metabolic, hormonal, thermoregulatory systems. Each of these systems can be affected by a number of genes and there are many interactions among the genes and between these genes and the environment.

Do Genes determine Champions?

By training you can make a slow donkey to a faster donkey, but you can never make a donkey to a race horse...that's why genes matter when it comes to sport.

Lee Sweeny, Geneticist

Olympic Gold begins with good Genes

At the 1960 and 1964 Winter Olympics Finnish sportsman *Eero M□ntyranta* won three gold medals in cross-country skiing. Throughout his career, he was suspected of blood doping. 30 years later, finnish scientists tested 200 members of his family and discovered that 50 of them, including Mäntyranta, were born with a rare mutation in the gene HCP (Hybrid Cluster protein) that produces the receptor for the hormone erythropoietin (epo).

The kidneys normally produce epo non-stop when oxygen levels in the body's tissues drop, as they do at high altitude. Epo commands the body to manufacture new red blood cells, which raises the blood's capacity to carry oxygen. Once oxygen regains its normal level in the blood, the epo

receptor should shut down epo production. But Mäntyranta's mutation turned off this crucial feedback, so his body kept making up to 25 per cent more red blood cells.

Tough his training programme wasn't radically different from those of his teammates and rivals, Mäntyranta had this distinct advantage, his muscles got more of the oxygen they needed for aerobic exercise, so he could ski faster for longer. But this genetic mutation is exceedingly rare. But as we all know, anyone can boost their red cells simply by adding more epo in their blood stream. In 1989, a injectable form of Epo, Epogen, was marketed, as a treatment of severe anaemia, and athletes worldwide, in their deceitful pursuit of glory, especially in the business of cycling, were quick to exploit the drug, even though such doping is banned in most sports. In the past EPO doping was accomplished by transfusion, today there are raising concerns about gen injections. Epo doping is dangerous, especially over long periods: high hematocrit (the proportion of the blood volume made up of red blood cells), concentrated thick blood.

In world class events where seconds separate winners and losers, the benefits of EPO are huge. In studies, endurance athletes on a treadmill outperformed their previous endurance levels after injecting with Epo, up to 30 seconds off a 20 minutes running time. Epo clearly results in greater cardiovascular stamina and the drug's allure is hard for many athletes to resist.

The gene-therapy techniques – still under development – use viruses to carry the epo gene into cells. In a study, where the epo gene was delivered to mice and monkeys, the boosted mouse hematocrits rose from 49% to 81%, while the monkey's hematocrits rose 40% to 70% (Human Gene Therapy, vol 8, p 1797). A single injection elevated hematocrits for over a year in mice and for 12 weeks in monkeys. But in some animals the red blood cell count was fatal and the high hematocrit level turned the blood to jelly.

Michael Phelps, eight gold medals in swimming at the Beijing Olympics in 2008, stands 193 cm and weighs 88 kg, with the broad shoulders and slim waist common to the elite swimmer. But, considering his body measurements a little closer, it becomes clearer why Phelps is dominating this sport.

He has an extended trunk and relatively short legs, a distinct advantage in the water. The inseam of his pants is reportedly 81 cm. Phelps could not become an Olympic Champion in track and field middle and long distance running, a sport wherre you need to be all legs, like former Olympic Champion Hicham El Guerrouj from Morocco, who is 175 cm, short trunk, but all legs (inseam of his pants 92 cm).

Phelps has double-jointed elbows, knees, and ankles, which allows him to bend himself like only few swimmers can. His size 14 feet are like giant fins. His arm-span is over two meters. And when we add to this the extraordinary work rate of his lungs and heart, Phelps appears almost superman, a different species from the rest of us. Most of all these characteristics are highly influenced by genes. Of course, he also trains extraordinarily hard. But so do others. To be an olympic swimming champion, a person's genes probably must first be preset for maximal athletic performance (Hseih et al., 2005).

The Insulin-like growth factor gene (IGF-1 gene), for example, located on chromosom 12, a gene with more than 80,000 bases, is responsible for skeletal and muscular development, producing a high number of amino acids, present in nearly all cell types of the body and the gene's polymorphism plays a crucial role in growth (Hertoghe et al., 2006). Scientists have already had some success getting this gene to "take" in animals and, unlike steroids, it increases the number of muscle cells, not just the size of them.

Interestingly other recent multiple olympic swimming champions from Sydney or Athens like Ian Thorpe from Australia (size 17 feet) or Peter van den Hoogenband from Holland have both similar characteristics. And in the sport of swimming it seems really that the best athletes in the world are a result of good genes and optimal training. Without a supercharged physiological system we can not become a world class athlete in this sport Macarthur et al., 2004).

Stretching the boundaries of normal physiology, elite athletes strive primarly for strength, speed, and endurance.

A cyclist, for example, needs great lung capacity, for superior endurance, and strives for a high VO2max, the maximum amount of oxygen the lungs can consume. Lance Amstrong, a 7 time

Tour de France winner, has an amazingly high VO2max, as well as the highest ever measured aerobic performance in a cyclist, two characteristics highly influenced by our genes.

Great cyclists generally have an extraordinary heart capacity. The average resting heart rate of a normal person is 66 to 72 beats per minute (bpm). A well trained endurance athlete has a resting heart rate of 40 bpm. Miguel Indurain from Spain, a five time Tour de France Winner and olympic gold medallist in 1996, recorded a resting heart rate of 28 bpm. In the mountain stages of the Tour de France, Indurain could take his pulse rate up to 190 bpm and drop it back to 60 on the descent within one minute.

Why are Jamaicans so good in sprinting?

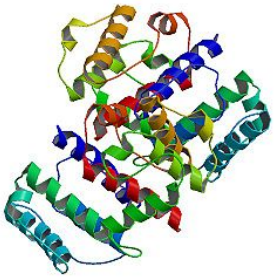
Jamaicans dominated the recent Olympic women's and men's sprint events, winning all 6 possible gold medals (100m, 200m, relay 4x100m). Naturally, these performances have provoked widespread speculation about the basis of Jamaica's and other population of West African Ancestry.

In recent years several studies have been published, examining performance gene frequencies among elite athletes. And we know today that more than 100 specific allelic variants of genes are known to produce favourable traits with respect to athletic performance (Wolfarth et. al, 2005).

The speed of a sprinter is determined in large part by physiology. There are two types of muscle fibers, slow-twitch and fast-twitch fibers. Slow-twitch fibers are more efficient in using oxygen, fast-twitch fibers fire more rapidly and generate more force.

Sprinters have a high percentage of fast-twich muscle fibers, fibers that contract quickly. The Gene ACTN3 – which produces a protein (Actinin-A, alpha-actinin-3)) in the fast-twitch muscle fibers has been linked to increase sprinting performance.

ACTN3 – Genomic Arrangement Functional Charistics



The ACTN3 gene is located on chromosome 11 and it spans approximatgely 16,407 bases of genomic DNA and is composed of 21 exons as shown in Figure 3.

Alpha-actinin-3

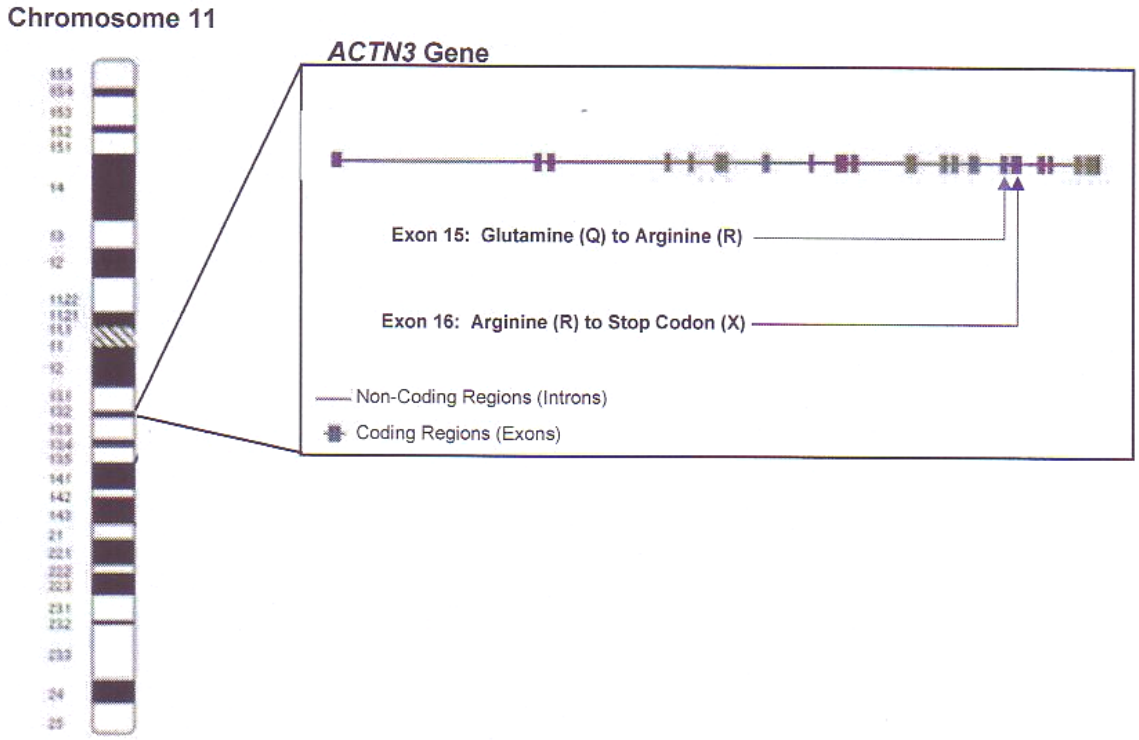


Figure 3 The *ACTN3* gene is located on the long arm (q) of Chromosome 11 on band 13.2. Exons 15 and 16 are the coding regions of the DNA that are transcribed into an mRNA molecule. A transition mutation in exon 15 has created the Q523R polymorphism whereas a nonsense point mutation in exon 16 has created the R577X polymorphism.

The expression of actinin-3 is limited to fast-twitch muscle fibers (Mills et al., 2001). Actinin-3 is part of the sarcomeric actinins, which are major components of the Z line, where its function is twolfold to connect with actin filaments and sustain the order of myofilaments and coordinate myofilament contraction (Yang et. al, 2003). The Z line (Figure 4) is an important structure within the sarcomere and its function is to provide structural support for the transmission of force when muscle fibres are activated (Wilmore et al., 2004).

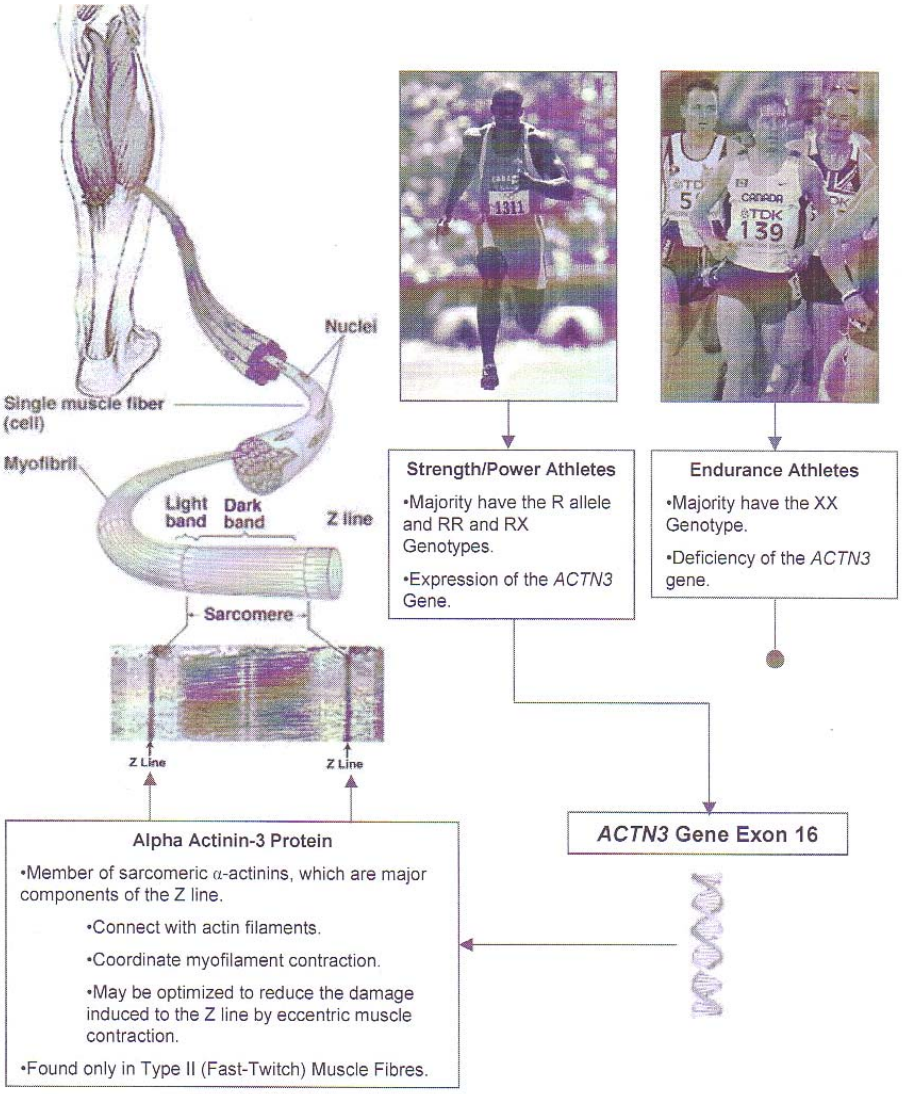


Figure 4 Effect of the *ACTN3* Gene on the Muscular System

Researchers believe that actinin-3 may be optimized to decrease the damage induced by eccentric muscular contraction (Yang et. al, 2003). This support is particularly important during forceful contractions, which are prevalent in fast twitch muscle fibers and is shown in Figure 4.

Now, how good is the scientific evidence? Does the Actinin-3 gene influence sprinting performance? And if so, does it explain the difference in explosive power between Jamaicans and the rest of the world?

The ACTN3 gene was first examined in 1999 (North et al., 1999) when a transition mutation was discovered in Exon 16 that resulted in a deficiency of the actinin-3 protein. Since then, among many other studies, have shown that the deficiency of this protein reduces the performances of athletes involved in speed/power events.

The University of West Indies together with the University of Glasgow are currently researching the genetic, nutritional, and sociological factors behind West Africa's sprinting success (Yang et al., 2003). The Actinin-3 protein, as we have seen, is found within the fast fibres of muscle – the cells that are required for generating rapid, forceful contraction in activities such as sprinting and weightlifting. Interestingly, the human ACTN3 gene comes in two forms in the general population: there is a normal, functional version called 577R, and a "defective" version called 577X, which contains a single base change that prevents the production of Actinin-3. People who have two copies, the 577XX version produce absolutely no Actinin-3 in their fast muscle fibres, on the other hand, people with two strong copies, 577RR, produce high amounts.

Preliminary findings suggest that 70 per cent of the Jamaicans habitants have the strong form of the ACTN3 gene, version, and a further 28 per cent of Jamaicans are heterozygous for the gene, with one single base changed – which has the same effect but to a lesser degree. The rest , by contrast, have the "null" form of the gene, two copies of the 577X version, that produces no protein at all. In control study of Australians, only 30 per cent were found with the speed protein Actinin-3 (Yang et al., 2003). At least one billion people worldwide must be completely deficient in Actinin-3 (Mills et al., 2001).

Studies have shown that the absence of Actinin-3 in XX individuals is detrimental to optimal muscle power generation, and is a handicap for athletes in speed and power events. This findings has since replicated in four separate athlete studies by groups in Europe, Australia and the US. And there is consistent evidence that Actinin-3 deficiency results in slightly higher endurance capacity. Several study groups have reported that XX individuals in general display lower muscle strength and reduced sprint and power performance. Another protein, actinin-2, produced by gene ACTN2, present in slow and fast twitch muscle fibers, is able to compensate for the deficiency of actinin-3 in XX individuals (North et al., 1999). Actinin-2 is 80 per cent identical to actinin-3 (Mills et al., 2001).

But interestingly these studies also suggust that the proportion of the variance in strength, sprint, and power performance between the "strong" form and the "null" form of the gene is only around a few per cent, but may have an effect under extreme conditions (eg. Elite sprinters). So for most of us, lazy slobs we are, this gene has a pretty trivial effect. However, these few per cent can make a striking difference at the elite level. Of the 51 Olympic-level sprint/power athletes analysed only a single individual was X/X (Yang et al., 2005).

So the absence of Actinin-3 means very little to most of us, but to a young athlete with Olympic dreams it could make all the differences in the world.

Does the ACTN3 gene explain Jamaican sprinting prowess?

The underlying argument here is intuitively simple:

1. Variation in the ACTN3 gene is strongly associated with elite sprint athlete status.
2. The "sprint" version of ACTN3 is more common in Jamaicans than in individuals of European ancestry.
3. Therefore this variant may well play a role in the increased sprinting prowess of Jamaicans relative to Europeans.

On the other side we have to consider:

1. The difference in frequency between Jamaicans and Europeans is great for the 577R version of the gene, the "strong" gene, but not as great as if you take into consideration the more appropriate comparison of individuals who have at least one copy of 577R. Including both, the R/R and the R/X individuals) it starts to look less impressive: 98% in Jamaicans to about 80% in Europeans. Only the complete absence, the X/X version is reiably associated with reduced sprint performance.
2. Usain Bolt – even in the first rounds of Olympic heats – was probably lined up against athletes who almost certainly all express Actinin-3, and it can't possibly explain the astonishing advantage her has over his competitors. There must be other factors at work.

Beyond the Jamaican "Gene for Speed"

There is no doubt that the ACTN3 gene is a minor piece in the Jamaican gold puzzle, but there must be many other factors at work. The ACTN3 gene may not disserve to the complex interplay of genetic and environmental factors required for top-level athletic performance. The ACTN3-centred argument dismisses the importance of Jamaica's impressive investment in the infrastructure and training system. Track and field has historically held a high place of honour in Jamaican culture and the 45 Olympic medals Jamaicans have now won in track and field, helps inculate a deep sense of national pride in this sport. The annual High school boys and girls athletics championchips is the national event in Jamaica, like Superbowl in the US. Many young Jamaicans have the powerful desire to use athletic success to lift themselves and their families out of poverty.

ACTN3 studies in other sports

In a Spansih study (Luca et. al, 2008), scientists studied the frequency distribution of the different version of the ACTN3 gene in 60 top-level professional soccer players. Altough there were a few notable exception, elite soccer player tend to have the sprint/power genotype of the gene, most of them the strong version. Similar results have been found in studies with the Russian national soccer team in 2006 (Santiago et al., 2008).

On the contrary, no association of the ACTN3 gene R577 polymorphism, the strong version of the gene, has been found with endurance performance in Ironmen Triathlons with hundreds of athletes and in consequence this version may have no significance for ultra-endurance performance (Collins et al., 2004).

Similar results have been shown in a large Russian study with endurance athletes and competitor in rowing. The 577X variants were significantly high in endurance-oriented athletes, the 577R variant was strongly associated with the rowers' competition results. In conclusion, ACTN3 577R polymorphism is associated with power athlete status in Russians today and is in practice in the selection of athletes in sports like weightlifting, ice hockey, and football (Ahmetov et al., 2008).

So, in conclusion there must be a significant association between ACTN3 genotype and athletic performance. Both male and female elite sprint/power athletes have significantly higher

frequencies of the 577R allele than do controls. This suggest that the presence of alpha-actinin-3 has really a beneficial effect on the function of sceletal muscle in generating forceful contractions at high velocity, and provides an evolutionary advantage because of increased sprint/power performance.

On the other hand, the variant R577XX, a truncated variant of the gene that blocks the production of actinin-3 protein is more common in successful endurance athletes, as research has found. In an Australian study (North et al., 2007) mice had been engineered to lack actinin-3. Then these "knockout" mice and ordinary mice with a functioning ACTN3 gene were put on a motorised treadmill, which spun ever faster until the luckless rodents were exhausted. The easy winner in this endurance test were the knockout mice, which were able to run on a average a third further than their counterparts.

The apparent reason for this: the loss of ACNT3's protein, as previously mentionned, is compensated by a different protein, called actinin-2, which shifted muscle metabolism towards a smoother, more efficient, aerobic pathway. And as a result, leg muscles could be contracted again and again, without tiring (North et al., 1999).

The ACE Gene and endurance sports

The gene, known as ACE gene, for angiotensin-converting enzyme, found in muscle, exists in two variants, with one 287 base pairs longer than the other. The longer of the two variants shows better performance in muscular endurance. Everyone has two ACE genes. Half of the polulation has one of each variant, while 25% have two short genes and 25% have two of the long variant (Montgomery et al., 2000).

ACE – Genomic Arrangement Functional Charistics

The ACE gene is located on chromosom 17 as shown in Figure 1. It covers approximately 20,546 bases of genomic DNA and is composed of 25 exons.

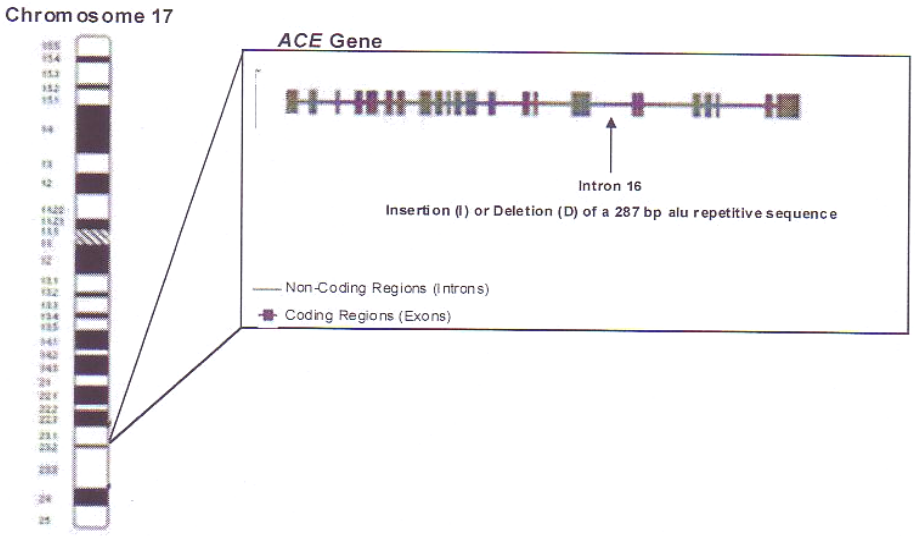


Figure 1 The *ACE* gene is located on the long arm (q) of Chromosome 17 on the band 23.2. The *ACE I/D* Polymorphism is characterized by an insertion (*I*) or deletion (*D*) of a 287 bp alu sequence at intron 16.

The Angiotension Converting Enzyme is an integral enzyme in the Renin-Angiotensin System (Figure 2), which is important in regulating blood volume, arterial pressure, and cardiac and vascular function (Tanriverdi, et al., 2005).

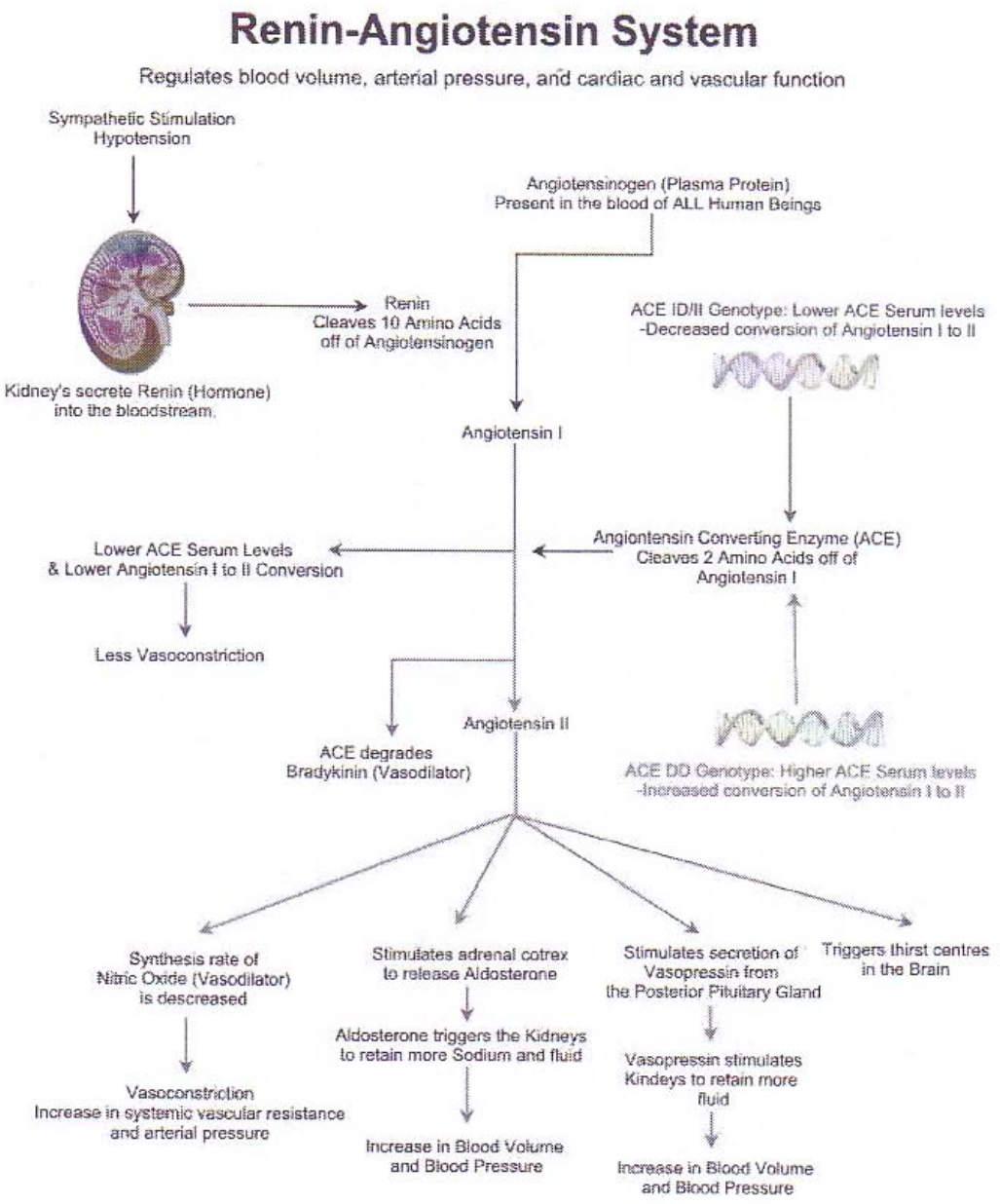


Figure 2 Effect of the *ACE* Gene on the Renin-Angiotensin System

The kidneys secrete the hormone renin into the bloodstream. Renin functions cleave a ten amino-acid protein off of the inactive liver peptide Angiotensinogen. The resulting intermediate peptide, Angiotensin I is then converted to Angiotensin II by ACE (Sonna et. al, 2001). Angiotensin II is a multifunctional peptide that acts indirectly to increase vasoconstriction, vascular resistence and

blood pressure and blood volume, and even stimulates the cerebral cortex to release the hormone aldosterone (Kem et. al, 1990).

Like for the ACTN3 gene, there are two version of the ACE gene. The ACE I/D polymorphism corresponds to the presence (I, insertion) or absence (D, deletion) on the chromosome band (Figure 1). Individuals, homozygous for the D-allele, have elevated ACE serum levels (Sonna et. al, 2001), Individuals, homozygous for I-allele, have lower ACE serum levels.

The ACE I/D Polymorphism has been examined extensively in the field of medicine for a large number of conditions such as Diabetes, Alzheimer's, and many cardiovascular diseases.

Relationship of Genetic variants of ACE Gene with Athletic Performance

The I allele is considered a favourable mutation because lower ACE activity results in less vasoconstriction and thus an increased delivery of oxygenated blood to the working muscles. Therefore, athletes that posses an I allele or the II genotype are thought to present a greater advantage in endurance activities such as running, cycling, swimming where the demand for oxygen is crucial.

Many studies with elite athletes have shown a difference of the I allele and II genotype in sprint/power versus endurance disciplines. In a group of British Olympic caliber athletes the frequency of the I allele increased from 35% in sprint athletes (>200m) to 65% in distance athletes (>5,000m), (Myerson et al., 1999). In a similar study Russian athletes (swimmer, skiers, triathletes, and track & field) there was an excess of the D allele (72%) in the short distance group and an excess of the I allele (73%) in the middle distance group (Nazarov et al., 2001).

In Italian athletes, based on Olympic performance and VO2max, the II genotype was found in 33% of Olympic aerobic athletes compared to only 5.3% in anaerobic athletes (Scanavini et. al, 2002). A finnish study (Rankinen et. al, 2000) where athletes – cross-country skier, runners – were also divided into groups based on maximal oxygen intake has shown similar results. These findings suggest that the I allele may be related to endurance athletes.

Studies on African endurance runners provide a mixed explanation to the huge success of their runners on the international level, probably due to environmental factors like altitude or

nutrition. In Kenya, the I allele frequency was similar in international (38%) and national (42%) level athletes and control subjects (38%), (Scott et al., 2006). Nevertheless in Ethiopians world class running power athletes the II genotype of ACE was found in 23% of male marathoners, compared to the control group with only 4.3%, the heterozygous type I/D was found in 43% of the athletes compared to 26% of the Ethiopian population.

Genetic Engineering – Molecular based Medicine

Mighty mice and super men

"Gene injections in mice, rats and monkeys can double muscle strength and speed...there are raising concerns that the virtually undetectable technology could or has already be used illegally to build super athletes, making them stronger, faster, bigger, more durable or otherwise inhumanly good."

Prof Lee Sweeny, Pennsylvania State University

Genetic engineering or genetic manipulation are terms that apply to direct manipulation of an organism's genes to alter the structure and characteristics of genes (Craig et al., 2004).

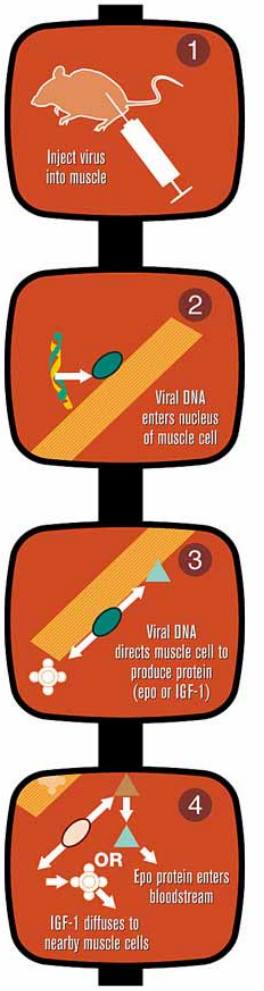
Today, gene therapy is a reality, albeit an imperfect one, and the tools of gene transfer have proven to be therapeutically effective in a number of clinical studies, including immunodeficiency diseases, cancer, genetic forms of retinal degeneration and blindness, alzheimer's and other diseases. Nevertheless, serious conceptual and technical problems continue to produce severe and unanticipated setbacks and adverse events.

Lee Sweeny is one of the leading researcher in this field and his studies on genetically engineered mice attracted the medical community, but also the sport-minded since he published his first set of results.

Using a common technique in which a normal copy of a gene is spliced into a carrier such as a virus and then injected into the body, Sweeny injected the muscles of his mice with the gene for insulin-like growth factor-I (IGF-I), a protein that promotes cell growth and cell repair. The mice gained anywhere from 15 to 40 per cent more muscle. When Sweeny injected rats doing weight training (they climb ladders carrying weights on their backs), they gained twice as much muscle as

rats doing only weight training. Neither the mice nor the rats lost any muscle as time passed. Nor where there any side effects.

Another study marked the debut of “marathon mice”, when another scientist created the strain by genetically engineering the switch that burns fat cells so it stayed on all time in the mice muscles. That allowed the mice to increase their slow-twitch muscle fiber, the type for good endurance. On a treadmill the mice ran one hour longer and twice the distance as normal mice.



In many ways, today’s elite sports already is a science fair. Athletes take dizzying arrays of pills and supplements, relentlessely hone training techniques and test cutting-edge equipments such as altitude tents. They employ psychologistes, nutritionists. Those are the athletes playing by the rules. Other use steroids, EPO, human growth hormones and other outlawed performance-enhancing drugs, as recent scandals with Major League Baseball, Tour de France and Marion Jones attest.

And now, in this shadowy world with its slippery ethics and gnawing suspicion of anyone who suddenly looks bigger or performs better than expected, genetic modification looms as the ultimate supplement. Improvement seems guaranteed and permanent. And there is no test for the moment to catch users. The World Anti-Doping Agency (WADA) is working with scientists to develop tests, annual budget 23 Mio Dollars, to be ahead of the gene curve instead of playing catch-up as WADA is with drugs.

Genetic Engineering

There are a number of ways through which genetic engineering is accomplished. Essentially, the process has five main steps:

1. Isolation of the gene of interest

2. Insertion of the gene into a transfer vector, or carrier (e.g. virus, bacteries)
3. Transfer of the vector/carrier to the organism to be modified
4. Transformation of the cells of the organism (e.g. virus multiplies)
5. Separation of the genetically modified organism from those that have not been successfully modified

One of the best known applications of genetic engineering is the creation of Genetic Modified Organisms (GMO's), such as food and vegetables. In athletes, genetic engineering could add traits that didn't exist.

Despite these success in animal studies, these studies are still only all sort of pointing in the direction of feasibility, and the approval tu use gene transfer in humans in even a limited way – for medical purpose – is probably still a few years away. Scientists believe that there is still a huge gulf between doing that in animals and in human beeings, but they also acknowledge that someone in sports has already tried gene transfer. The problem in human is that viruses carring genes are most of the time recognized and destroyed by the immune system. And another big problem is that there is no way to turn the gene off once it has been inserted. And the gene therapy could also trigger cancer. One seemingly successful French trial for treating severe combined immunodeficiency disorder was recently halted when some of the 11 patients developed leukaemia (Gene Therapy, vol 5, p 665, 2008).

But Gene transfer will infiltrate sports because athletes by nature are risk takers. Those who use illaegal drugs do so despite proven long-term side effects. Many athletes face enormous national pressure to win, and the financial rewards can be huge. And genetic manipulation currently is undectable. Plus, the stigma attached to gene transfer might fade as enhancement (Viagra, cosmetic surgery) becomes more accepted by society in general. The only surefire way to test for genetic modification of an athlete's muscle at this time is a muscle biopsy, but you have to find the muscle where the gene has been injected.

No turning back

"Gene therapy may well be used in race horses well before humans, because if someone kills a horse they are not going to prison for life, the risks are less...the potential gains are probably even greater."

Richard Pound, President Wada, 1999-2007

The human Genome project provided a genetic road map to the body. Researchers and athletes know now which athletic-enhancing functions are triggered by which of our 30,000 genes.

Gene transfer combined with genetic testing will have a profound impact on pro sports. Already, an Australian Company offers a test where parents can find out if their child would better be suited to speed and power events, or to endurance events.

The inevitability of athletic abuse hasn't made scientists questions or stop what they are doing. The potential medical benefits of their work are extraordinary. But the history of sports doping follows a disquieting pattern: Legitimate advances in medicine are hijacked by rogues who take something intended as therapy for the sick and use it as enhancement for healthy athletes.

Steroids were developed for starvation victims and people suffering from kidney failure. EPO was a treatment for anemia, Human growth hormone is given to children with dwarfism. Surprisingly biology is not so difficult, and a experienced molecular biologist can make the virus and isolate the genes and doing foolish things at the genetic level as they are at the drug level.

The East German sports machine, which systematically forced its athletes to take large amounts of steroids, surely would have tried systematic gene doping by now, were it still intact. Today, other experts point to entrepreneur-friendly laissez-faire Russia, or China, with flimsy regulations and lax oversight.

But according to the world's leading scientists, the magical altering of the genes is very complex, there are interactions among different genes, and there are interactions among genes and the environment. And at this time it seems that science and sports medicine is still lagging behind in terms of utilizing the advances in genetic and genomic technologies. Nevertheless, the gene genie is bearing down on sports. Sooner or later, it's going to make it to the starting line.

Detecting abuse won't be easy. The big problem is that proteins made by engineered genes look identical to the ones the body makes naturally. About the only way scientists might detect illicit gene therapy would be to find traces of the virus that delivered the gene. If they were looking for the IGF-1 gene (growth hormone) or the Gata-1 gene (Epo), they could take a biopsy from the muscle and look for viral DNA, but they would have to know exactly where it was put in. Another approach is to look for abnormally high levels of a gene's product but you have to repeat the biopsy after 12 hours to compare the levels. But no one seriously expect athletes to line up for muscle biopsies before they go out to compete at the Olympics.

Nevertheless, the IOC together with its WADA Gene Doping Panel hopes to crack down on "gene doping" in 2010. Wada (annual budget of 23 million dollars) is intensively working with the world's leading geneticists to find effective screening technics. These scientists actually study a number of the side effects that occur with changes to genes and to metabolism. If researchers can put these together to create a "signature", eventually it may be possible to detect this signature in saliva samples, exactly the same way that DNA technology has added so much in forensic science and crime detention (WADA Doping Symposium 2008, Saint-Petersburg, Russia).

But if history is any guide for this problem, scientists will have a tough time staying ahead of the cheats and that is nothing new. A lot of money has been spent to detect drugs, but drug test are easy to circumvent and probably many of the track and field recordsset in the past 30 years, for example, have been drug aided.

What makes anyone think that's going to change?

Conclusion

How many genes play a role in sports talent? We don't know for the moment. Today, scientists believe that about 200 genes must have some positive association with fitness-related performance. We know that genetics influences many factors such as cardiorespiratory function, muscle biochemistry, body size and motor skills and even nerve communications.

But as we know, there are more than 25,000 genes in the genome, so we are just scratching the surface. And in sports performance there is a wide range of factors. Sports performance is so

complex. As a general rule, genetic influences are stronger on the structural components of the body than on the functional components, which can be influenced more by training and other environmental factors.

For the moment ACTN3 is probably the most consistently associated of the genes studied so far and the most consistently associated with sports-related performances. People who are the XX-genotype do not have actinin-3 in their muscles, and in consequence, their muscles won't work as well, and that will prevent them from reaching the upper echelon of power performance. This has been indicated in a great number of studies.

The ACE gene studies are also very interesting, but more conflicting, the findings are not as consistent as for the ACTN3 gene. But there are many more genes that could be useful to athletes. Today, we know 16 mitochondrial genes in which sequence variants have been shown to influence relevant performance phenotypes like the IGF-1 or insulin growth factor gene, the HCP Epo gene, the MGF or mechano-growth factor gene, a different form of the IGF-1 gene, that could limit fatigue and improve muscle repair, or the AMPK gene (5'AMP-activated protein kinase) that regulates cellular ATP, affects how muscles accumulate glycogen and therefore impacts endurance. Studies worldwide are on the way.

Although genetic background can influence one's success in a particular sport, this background is probably too complex for the moment to be fully known or understood. Genes do influence the initial level of one's characteristics – phenotypes – as well as how fast and how much they can change in response to training, nutrition, and other environmental factors. The best athletes in the world are probably a result of good genes and optimal training.

Athletes who have immediate success in a sport probably have relatively high qualities of at least some of the genetically determined phenotypes required to be a champion in that sport. Superior responders to sport participation probably have early success and positive feedback from competition.

Sports genetics can help us to understand how our biological individuality relates to sports and how it can be harnessed to provide a competitive advantage. Coaches can and do already select candidates based on the characteristics required for success in that sport. The genes influence many of

these characteristics. But champions at the elite level must be experts in tactics and technique in addition to possessing the necessary genetically determined attributes for success in their sports.

References

Ahmetov II, Druzhevskaya, Astratebkova, Rogozin, 2008. Association of the ACTN3 R577X polymorphism with power and endurance athletes in Russia. *Eur J Appl Physiol. 2008 Aug; 103(6):631-34.*

Bouchard C., A.S. Leon, D.C. Rao, J.S. Skinner, J.H. Wilmore, and J. Gagnon, 1995. The Heritage Family Study: Aims, design, and measurement protocol. *Med Sci Sports Exerc. 27:721-29.*

Bouchard C., R. Malina, L. Pérusse, 1997. Genetics of Fitness and Physical Performance. *Champaign: Human Kinetics, 1-400.*

Bouchard C., P. An, T. Rice, J.S. Skinner, J.H. Wilmore, J. Gangnon, L. Pérusse, A.S. Leon, D.C. Rao, 1999. Familial aggregation of VO2max response to exercise training. *J Appl Physiol. 87: 1003-1008.*

Churchill, F.B. 1974. W. Johannson and the genotype concept. *J History of Biology 7: 5-30.*

Collins, M., Xenophontos, S.L., Cariolou, M.A., Mokone, G.G., Hudson, D.E., Anastasiades, L., Noakes, T.D. 2004. The ACE gene and endurance performance during the South African Ironman Triathlons. *Medicine & Science in Sports & Exercise. 36(8): 1314-1320.*

Hertoghe, T., 2006. *The Hormon Handbook: IGF-1. pp 53-75*

Hseih, S.S., Chiu, L.L., Hseih, L.L. 2005. ACE I/D and ACTN3 R577X Polymorphism in elite swimmers. *Medicine & Science in Sports & Exercise. 37(5): 166*

Kem, D.C., Brown, R.D. 1990. Renin – from the beginning to the end. New England Journal of Medicine. 323: 1136-37.

Macarthur, D.G., North, K.N. 2004. Genes and Elite Athletes. *Chemistry in Australia, August 2004.*

Mills, M., Yang, N., Weinberger, R., Van der Woude, D.L., Beggs, A.H., Easteal, S., North, K. 2001. Differential expression ot the actin-binding proteins in different species. *Human Molecular Genetics. 10(13): 1335-46.*

Myerson, S., Hemmingway, H., Budget, R., martin, J., Humphries, S., Montgomery, H. 1999. Human angiotensin I-converting enzyme gene and endurance performance. *J of Appl Physiol 87: 1313-16.*

Nazarov, I.B., Woods, D.R., Montgomery, H.E., Sneider, O.V., Kazakov, V.I., Tomilin, N.V. 2001. The angiotensin converting enzyme I/D polymorphism in Russian athletes. *European J of Human Genetics. 9: 797-801.*

North, K.N., Yang, N.,Mill, M., Easteal, S., Beggs, A.H. 1999. A common nonsense mutation results in actinin-3 deficiency in the general population. *Nature Genetics. 21: 353-4.*

Rankinen, T., Perusse, L., Rauraama, R., Rivera M.A., Wolfarth, B., Bouchard, C. 2004. The Human Gen Map for Performance and Health-related Fitness Phenotypes: The 2003 Update. *Medicine & Science in Sports & Exercise. 36(9): 1451-69.*

Rankinen, T., Simoneau, J.A., Rauraama, R., Rivera M.A., Wolfarth, B., Bouchard, C., Perusse. L., Boulay, M.A. 2000. No association between the angiotensin converting enzyme ID polymorphism and elite endurance athlete status. J of Applied Physiol. 88: 1571-75.

Santiago, C., gonzalez M., Serratosa L., Meyer T., Lucia A. 2008. ACTN3 genotype in professional soccer player. *Br J Sports Med, 2008 Jan, 42(1): 71-3.*

Scanavini, D., Bernardi, F., Castoldi, E., Conconi, F., Mazzoni, G. 2002. Increased frequency of the homozygous II ACE genotype in Italian Olympic endurance athletes. *European J of Human Genetics. 10: 576-7.*

Scott, R.A., Moran, C., Wilson, R.H., onywera, V., Boit, M.K., Goodwin, W.H., Gohlke, P., Payne, J. 2005. No association between ACE gene variation and endurance athlete status in Kenyans. *Comparative Biochemistry and Physiology. 141: 169-175.*

Sonna, L.A., Sharp, M.A., Knapik, J.J., cullivan, M., Angel, K.C., Patton, J.F. 2001. Angiotensin-converting enzyme genotype and physical performance in US Army athletes. *J of Appl Phisiol. 91: 1355-63.*

Tanriverdi, H., Evrengul, H., Tanriverdi, S., Turgut, S., Akdag, B., Semiz, E. 2005. Improved endothelium dependent vasodilation in endurance athletes and its relation with ACE I/D polymorphism. *Circulation Journal. 69: 1105-10.*

Wilmore, J.H., Costill, D.L. 2004. Physiology of Sport & Exercise, *3rd edition, Champaign: Human Kinetics.*

Wolfarth, B., Bray, M.S., Hagberg, J.M., Perusse, L., Rivera, M.A., Roth, S.M., Bouchard, C. 2005. The Human Gene Map for Performance and Health-related Fitness Phenotypes: The 2004 Update. *Medicine & Science in Sports & exercise. 37(6): 881-903*

Yang, N., MacArthur, D.G., Gulbin, J.P., Hahn, A.G., North, K. 2003. ACTN3 Genotype is associated with human elite athletic performance. *American J of Human Genetics. 73: 627-31.*

Yang, N., MacArthur, D.G., Wolde, B., Onywera, V.O., Boit, M.K., Wilson, R.H., Scott, R.H., North, K. 2005. ACTN3 genotype is not associated with elite endurance athlete status in Kenyans and Ethiopians. *Medicine & Science in Sports & Exercise. 37(5): 472.*