Tour de France Champions born or made: where do we take the genetics of performance?

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Abstract (200 words)

Cyclists in the Tour de France are endurance specialists. Twin and family studies have shown that approximately 50% of the variance in a number of performance related phenotypes (whether measured at baseline, *i.e.* natural talent, or in response to training) including those important to cycling can be explained by genetic variation. Research into the specific genetic variants that are responsible has identified over 200 genes containing common genetic variants involved in the genetic predisposition to physical performance. However, typically these explain only a small portion of the variance, perhaps 1-2% and collectively they rarely explain anything approaching the 50% of the variance identified in the twin and family studies. Thus, there is a gap in our understanding of the relationship between heritability and performance. This gap may be bridged by investigation of rare variants or epigenetic variation or by altering study designs through increased collaborations to pool exiting cohorts together. Initial findings from such efforts show promising results. This mini-review will touch on the genetics and epigenetics of sporting performance, how they relate to cyclists in the Tour de France and where best future efforts may be directed as well as discuss some preliminary research findings.

Keywords (3-6 words)

Genetics; Epigenetics; Cyclists; Elite athlete cohorts; PowerGene; GAMES

Main text

Introduction

Since at least the time of the Ancient Greeks humans have challenged each other in competitive performance tasks. Concomitantly scholars have attempted to identify the determinants of performance and thus methods to improve performance. Aristotle, in his Nicomachean Ethics (Aristotle, 2002), wrote, “both excessive and insufficient exercise destroy one's strength, and both eating and drinking too much or too little destroy health, whereas the right quantity produces, increases or preserves it.” Modern day sports science maintains these efforts and is in part responsible for the continued improvements in performance in most sports that we see to the present day. In cycling we have seen improvements in the technology of the bicycle, the athlete’s diet, nutritional strategies during the race and in types and management of training to name only a few of the areas of advancement. Competitors in the Tour de France are supported by a large team of experts including Sport Scientists, Physiotherapists, Medics and Nutritionists. However, given the right team, resources and training, the question remains whether anyone can win the Tour de France or whether champions are born with some innate genetic advantage over others.

The Tour de France is a gruelling endurance event. The cyclists who take part are endurance experts. Typically the race covers 3200-4000 km and contains long flat stages, shorter individual time trials and uphill stages. Although the cyclists may specialise, or be more suited to, one type of terrain, they have to cover all three types of terrain. Their characteristics are reviewed in Lucia, Hoyos, & Chicharro (2001). In summary, typically they will all have high maximal power output (>500 W) in incremental tests with 1 minute increments, high power to weight ratio (6-7.5 W/kg), high maximal oxygen uptake ($\dot{V}O_{2max}$; 70-80 ml/min/kg) and a high anaerobic threshold (~90% $\dot{V}O_{2max}$) although the precise values vary depending on their specialism. Physiologically, they are likely to have low body fat (8-10%), large hearts

(152 g/m^2 mean ventricular mass index), large arteries (~13% larger carotid arteries), higher skeletal muscle type I fibre content (Coyle et al., 1991) and increased mitochondrial volume (Rodríguez et al., 2002). Whilst many of these characteristics may be altered by training (Rivera-Brown & Frontera, 2012) several have also been shown to be influenced by genetics (see Wolfarth et al., 2014 for review). Thus, rather than ask whether Tour de France champions are born or made it is more appropriate to ask what the extent is of the influence of genetics on the making of Tour de France champions.

Genetic Variation, Heritability and Performance

The Human Genome Project was completed over a decade ago (Lander et al., 2001). However, we all carry slightly different versions of that DNA sequence and in terms of understanding human physiology the sequence differences between us are as interesting as the basic sequence itself. Subsequent projects such as the HapMap (International HapMap Consortium, 2005) and 1000genomes (Abecasis et al., 2012) projects have provided information on the extent of the variation between individuals. Ultimately, it is clear that whilst human DNA sequences are highly similar (~99%) there are a large number of sites in our DNA at which we vary (~38 million); and, that the rate of variation at these sites has a wide range with some variants very common in the population and others very rare. For example, the minor allele of *alpha-actinin-3* variant rs1815739 has a global frequency of 40% whilst the minor allele of the *erythropoietin receptor* variant rs121917830 has a global frequency of <0.001%.

To understand how these genetic variants relate to cycling performance or to sports performance in general we also need to assess human performance variation and relate that to the genetic differences. However, few studies specifically investigate cyclists. In a general sense, it is widely recognised that humans display a large variation in physical performance (e.g. Bouchard et al., 1998). We also think of some individuals as naturally talented and

others as lacking in talent (Hyllegard, Radlo, & Early, 2001; Williams & Reilly, 2000). Similarly, we see some individuals make large gains in performance with training whilst others show little or no response to training (Bouchard et al., 1999). Furthermore, individuals often excel at endurance based sports or power based sports, but rarely both. In part these differences will result from differing training modalities (*i.e.* more sprint / power or endurance) and opportunities for sports participation. However, talented individuals often come from talented families (De Moor et al., 2007) and whilst families share many aspects of their environments, they also share known amounts of their DNA depending on the relationship between the specific individuals in question. If genetic variation is even partially responsible for the physiological characteristics important for cycling, then unique combinations of variants are likely to have the potential to predispose an individual towards elite cycling ability.

Twin and family studies make use of the known quantity of shared DNA to partition the variance in performance that can be explained by environmental factors or by genetic factors. A British twin study, which included a small number of cyclists, found that athlete status runs in families and has a large genetic component (De Moor et al., 2007). If we focus on endurance capacity, a key aspect of cycling performance, the classic family study is the HERITAGE study (Bouchard et al., 1998, 1999). Bouchard and colleagues recruited 98 families comprised of 481 sedentary individuals to a training study. They measured their maximum aerobic capacity ($\dot{V}O_{2max}$), then trained these individuals 3 times a week for 20 weeks before measuring their $\dot{V}O_{2max}$ again. The average gain in $\dot{V}O_{2max}$ was approximately 0.4 L/min although there was a very large range of values from little or no gain to gains over 1 L/min. Due to the relatedness of the family members they were able to estimate that approximately 50% of the variance in $\dot{V}O_{2max}$ could be explained by genetic variation (whether measured at baseline, *i.e.* natural talent, or in response to training). This implies that genetic variation

is at least as important to performance as everything else put together, *i.e.* lifestyle, diet, training, facilities, *etc*.

Common Genetic Variants

Research into the specific genetic variants that are responsible for this genetic portion of the variance has identified over 200 genes containing common genetic variants involved in the genetic predisposition to aspects of physical performance (Wolfarth et al., 2014). Work on the genetics of sporting performance has involved cohorts of elite level athletes from around the globe and from a variety of sports. It includes Ethiopian and Kenyan endurance runners, track sprinters from Jamaica and the USA and both endurance runners and sprinters from Australia, Russia, and Japan. However, although several of these cohorts include endurance cyclists, typically the number of cyclists is small and very little research has been done directly on the genetics of cycling performance. Contrast the number of performance related genes (>200) with the less than 20 genes that have been investigated in cohorts containing cyclists (Table 1). Cyclists are often included because many of the characteristics important to cycling performance, such as high $\dot{V}O_{2max}$ or high anaerobic threshold, are common to other endurance sports. Thus, they are included as part of an endurance sports group with little more detailed information. Furthermore, it is rare for these cohorts to include quantitative measurements of all the key performance characteristics known to be important to cycling performance. Obtaining quantitative measurements requires more of the athletes' time and thus makes recruitment more challenging. Consequently, most of what is known about the genetics of cycling performance is inferred from other sports requiring similar physiological traits. More, larger studies including elite cyclists are warranted.

Perhaps the best known example of a performance variant is alpha-actinin-3 (ACTN3) R577X (rs1815739) which has been strongly linked to sprinting ability (Moran et al., 2007; Yang et al., 2003) and less conclusively with endurance ability (Alfred et al., 2011). ACTN3 is a muscle

structural protein mostly found in type 2 fibres. It is an unusual variant in that the X-allele is a nonsense allele and XX homozygotes carry no functional ACTN3 whatsoever despite being relatively common (approximately 16% of the global population, ranging from approximately 1 to 30% in various populations). These individuals survive due to functional redundancy between ACTN3 and alpha-actinin-2 (ACTN2) although that redundancy must be incomplete since XX homozygotes are significantly less likely to become elite sprinters. This and similar findings have been replicated in many cohorts (Berman & North, 2010). Although a small number of studies find no association with sprint / power performance (e.g. Rodríguez-Romo et al., 2013), it is likely that this can be explained by statistical chance or subject differences. Conversely, the X-allele has been linked to endurance capacity (Yang et al., 2003) although somewhat less conclusively (Alfred et al., 2011). Three studies (Table 1) have investigated the association between ACTN3 genotype and endurance cycling hypothesising that they would find an over-representation of the X-allele in elite cyclists. However, two studies found no association and the third found an under-representation of the X-allele in cyclists.

Typically, these common genetic variants, including ACTN3 R577X, explain only a small portion of the phenotypic variance, perhaps 1-2%. Such small effects are difficult to identify without very large cohorts. This is compounded by the fact that case-control approaches assume that the controls have little or no genetic predisposition towards athleticism; however, it is much more likely that they contain a number of genetically predisposed individuals who are simply inactive and therefore not meeting their athletic potential (Tucker & Collins, 2012). Furthermore, predisposing variants are often identified in small cohorts without replication of the findings in secondary cohorts (see Pitsiladis et al., 2013 for review). Thus there is a risk that many of the variants identified so far may be false positive artefacts of small cohorts with only the most robustly replicated variants, such as ACTN3 R577X, being true positives. In part, this problem is due to the difficulty in recruiting large enough numbers of elite athletes who are a very small minority of any population. Furthermore, collectively

the genetic variants rarely explain anything approaching the 50% of the variance identified in the twin and family studies. Thus, a gap in our understanding of the relationship between heritability and performance exists.

Rare Genetic Variants

One possible explanation for this gap in understanding is that we have yet to fully consider the influence of rare genetic variants on sports performance. Until recently, studies into the genetics of quantitative traits concentrated on common genetic variants; that is variants with a minor allele frequency in the population of > 1%. The rationale for this was partly based on the common variant common disease hypothesis (Lander, 1996) which postulates that quantitative phenotypes with a classic bell-shaped distribution are the result of the influence of many 10s-100s of genes, each with a small influence on phenotype. However, there were also practical and commercial reasons. Practically, studies into rare variants needed very large cohorts of unrelated individuals to identify enough rare homozygotes to study. Also, due to their rarity, not all rare variants have necessarily been identified by current DNA sequencing efforts, even now. Commercially, biotechnology companies generally produce technologies that can be sold to mass markets to maximise their profits thus the focus remained on common variants. However, with the ever decreasing cost and increasing speed of next generation DNA sequencing (NGS) (Wetterstrand, 2014) it is now feasible to perform whole genome DNA sequencing on large cohorts of individuals thus identifying unknown rare variants and allowing testing of their associations with quantitative phenotypes.

Rare variants are already known to influence performance; although the best example was not identified by modern NGS but instead by the more traditional and slower genetic method of identifying a disease-carrying family and following the disease through the generations of that family. Nonetheless this example highlights the potential of the infinitely higher throughput method of NGS to identify additional rare variants with significant influences.

Eero Mäntyranta was a Finnish cross county skier in the 1960s. Cross country skiers are also endurance experts sharing many physiological characteristics with cyclists. Eero Mäntyranta collected 7 Olympic medals, 5 World Championship medals and 9 domestic championship medals making him a truly World class athlete (Olympic.org, 2014). Several members of his extended family suffered from a disease called familial erythrocytosis-1 (ECYT-1) due to a rare variant (rs121917830) of their erythropoietin receptors (de la Chapelle, Träskelin, & Juvonen, 1993). Collectively the related diseases of ECYT1-4 occur at a frequency of less than 1 in 100,000 (Hussein, Percy, & McMullin, 2012) so rs121917830 is a rare variant by any standard although precise allele frequency information on rs121917830 is not available. Normally, erythropoietin (EPO) is produced in response to low oxygen levels. It activates the EPO receptor (EPOR) resulting in the production of more red blood cells and thus an increase in the oxygen carrying capacity of the blood. Individuals with ECYT-1 have variant EPORs that are effectively hypersensitive to EPO; thus they have an increased red blood cell count and the oxygen carrying capacity of their blood can be increased by up to 50%. The extra blood cells thicken their blood putting them at risk of abnormal blood clots which can cause life threatening complications; however, if they exercise, the additional oxygen carrying capacity gives them an advantage at endurance events; similar to the effects of injecting the drug EPO (Durussel et al., 2013). It is this kind of natural variation that creates the necessity for a complex biological passport rather than a simple permissible threshold. Such a variant would also likely be of benefit to individuals involved in elite cycling. Paradoxically, those carrying rs121917830 variation are likely to derive less, if any, benefit from the illicit use of EPO.

Rare variants are expected to have larger influences on phenotype than common variants in part explaining why they remain rare since larger influences on phenotype are likely to be less well tolerated. So far, rare variant studies have concentrated on major human diseases such as cancer (Stadler, Schrader, Vijai, Robson, & Offit, 2014) or cardiovascular disease (Peloso et al., 2014). However, typically these rare variants have been in the same genes as

the established common variants and have not furthered our understanding of these phenotypes as much as was anticipated. It seems likely that when NGS is applied to elite cyclists or performance phenotypes that some rare variants with important influences will be identified although it seems equally unlikely that this will be the whole story.

Epigenetic Variation

Another source of heritable variation that may help explain the gap in our understanding is through epigenetic coding. Physiological epigenetics is a rapidly developing field with great promise. Epigenetics includes histone modifications, DNA methylation and RNA interference by non-coding RNAs such as microRNA (miRNA). This review will only cover miRNAs although both histone modifications and DNA methylation are involved in control of gene expression and are also likely important to sports performance (Ling & Rönn, 2014; McGee, Fairlie, Garnham, & Hargreaves, 2009). Like genetic variants, epigenetic modifications are heritable (Rissman & Adli, 2014); however, unlike genetic variants, they are also malleable within an individual (Baggish et al., 2011; Barrès et al., 2012). Thus, understanding epigenetic modifications may not only help us understand which individuals have the most sporting potential but also help understand how they can be manipulated through appropriate training and dietary regimes that may help improve performance.

The traditional view of molecular biology, encapsulated in the central dogma (Crick, 1970) held that proteins were easily the most important functional molecule in a cell and that RNA was mostly an intermediate step between DNA and proteins (excepting tRNA and rRNA). However, recent data from the ENCODE project (Bernstein et al., 2012) suggests that whilst approximately 75% of the genome is transcribed into RNA (Djebali et al., 2012) only a small proportion of that (1-3%) is directly involved in protein coding (Bernstein et al., 2012). Thus the vast majority of RNA is non-protein-coding. However, much of this non-protein-coding RNA appears to have functions which are only now beginning to be explored. A number of

recent studies in exercise genomics have recognised the importance of non-coding RNAs, specifically miRNAs (Kirby & McCarthy, 2013). miRNAs are involved in post-transcriptional control of messenger RNA (mRNA) either by inhibiting their translation, or by targeting mRNAs for degradation (Guay, Roggli, Nesca, Jacovetti, & Regazzi, 2011). Each miRNA can bind multiple mRNAs and each mRNA can be bound by multiple miRNAs; therefore, miRNAs comprise a highly complex network of regulators that fine tune gene and protein expression. miRNAs have been shown to be involved in muscle cell development (Luo, Nie, & Zhang, 2013), respond to exercise both acutely and chronically (Russell et al., 2013) and be predictive of response to training (Davidsen et al., 2011). Intriguingly, miRNAs also have been found at stable levels in plasma (Chen et al., 2008; Mitchell et al., 2008). Plasma miRNAs have been shown to both respond to exercise (Baggish et al., 2011; Davidsen et al., 2011) and be dysregulated in disease (Chen et al., 2008; Mitchell et al., 2008). There also is growing evidence that plasma miRNAs are taken up by target tissues and may be involved in cell-cell communication (Rayner & Hennessy, 2013). By nature of their location in the circulation, plasma miRNAs have the potential to fine tune the gene expression and protein translation of multiple genes in multiple tissues and thus may have influence in coordinating the whole body response to exercise such as cycling. miRNAs, mRNA and proteins comprise a very complex system regulating the function of cells. This type of complexity can only be captured in systems biology models and future research should endeavour to create such models for exercise phenotypes to build a complete understanding of the determinants of cycling performance and sports performance in general.

Elite Athlete Cohorts

A final source of the gap in our understanding of the heritability of cycling and exercise performance may be due to the specific cohorts and phenotypes within those cohorts that have so far been used. Collecting large cohorts is time-consuming and elite athletes are rare;

elite cyclists even rarer. Thus, collecting large enough numbers of them for comprehensive studies is difficult. Furthermore, quantitative measurements allow the use of more powerful statistical techniques. However, elite athletes have strict training regimes and are generally unwilling to come to the laboratory for detailed physiological testing, training interventions or invasive procedures that may impede their training in the ensuing days. A partial answer to this may be to pool our efforts by combining existing cohorts of athletes for genome wide association studies (GWAS) or NGS studies with subsequent replication in existing secondary cohorts. Initial findings from such efforts show promising results. With this objective in mind, two consortia have recently been formed to conduct the first GWAS of elite athletic performance using existing athlete cohorts, summarised in Table 2 (and described in Pitsiladis et al., 2013): the PowerGene consortium and GAMES Consortium (Genomic Variants Associated with Elite Endurance Athlete Status). Preliminary findings show promising odds ratios and a trend towards the conventional GWAS significance threshold at $p \leq 5 \times 10^{-8}$. Further validation of these signals in independent cohorts will be required, and any replicated SNPs taken forward for fine-mapping / targeted re-sequencing and functional studies to uncover the underlying biological mechanisms. Both of these consortia are now part of the much larger Athlome Consortium (http://www.athlomeconsortium.org/) which will facilitate replication and further analyses of their signals as well as foster new discoveries.

Conclusions

To move performance genetics and in particular cycling performance genetics forward we need: (1) to collect larger cohorts of elite athletes and in particular cyclists as well as persuade them of the importance of collecting detailed phenotypic information; (2) to collaborate to pool existing cohorts together; (3) when possible collect additional samples such as blood, plasma and tissue that will allow future epigenetic analyses; (4) to pursue

cutting edge technologies such as next generation sequencing, transcriptomics and proteomics; and (5) to integrate all these results into systems biology models.

Finally, can anyone become champion of the Tour de France? For this to happen an individual must possess the right genetic and epigenetic variation to display natural talent at cycling, the right genetic and epigenetic variation to be able to respond to appropriate training and do the training with the right team supporting them in the right way. This is not an either / or situation. Champions of the Tour de France are both born and made: genetic and epigenetic variations provide the potential in some individuals but they must then unlock that potential with appropriate training and lifestyle.

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Table(s) with caption(s) (on individual pages)

GENE	VARIANT	STUDY DESIGN	ATHLETES	ETHNICITY & GENDER	ATHLETES (CYCLISTS)	CONTROLS	ASSOCIATION (REFERENCE)
ACE	rs4646994 (intron 16 indel)	Case-control	Professional cyclists, long-distance runners and handball players	Spanish males	60 (25)	400	I-allele over-represented in athletes compared to controls (Alvarez et al., 2000).
		Case-control	Professional cyclists and Olympic-class endurance runners	Spanish males	77 (50)	119	DD genotype over-represented in cyclists compared to controls or runners. D-allele over-represented in cyclists compared to runners (Lucía et al., 2005).
		Case-control	Mixed endurance and power or sprint sports	Iranian males	156 (37)	163	D-allele over-represented in cyclists compared to controls (Shahmoradi, Ahmadalipour, & Salehi, 2014).
		Case-control	Professional cyclists, Olympic-class endurance runners and World class rowers	Spanish males	141 (50)	123	II under-represented in rowers compared to whole cohort (Muniesa et al., 2010).
		Case-control Quantitative muscle power	Endurance, power and mixed athletes	Lithuanian males and females	193 (12)	250	DD genotype over-represented in endurance compared to power athletes. DD genotype lower power than II genotype (Ginevičienė, Pranckevičienė, Milašius, & Kučinskas, 2010).
ACTN3	rs1815739 (p.R577X)	Case-control Quantitative $\dot{V}O_{2max}$ data	Professional cyclists and Olympic-class endurance runners	Spanish males	102 (50)	123	No association with endurance (Lucia et al., 2006).
		Case-control	Endurance-oriented athletes including road cyclists	Russian males and females	456 (34)	1211	C-allele (577X) under-represented in endurance athletes (Ahmetov, Druzhevskaya, et al., 2010).
		Case-control	Professional cyclists, Olympic-class endurance runners and World class rowers	Spanish males	141 (50)	123	No association with endurance (Muniesa et al., 2010).
		Case-control Quantitative muscle power	Endurance, power and mixed athletes	Lithuanian males and females	193 (12)	250	No association with athlete group or power (Ginevičienė, Pranckevičienė, Milašius, & Kučinskas, 2010).
ADRB3	rs4994 (p.W64R)	Case-control	Professional cyclists, Olympic-class endurance runners and power athletes	Spanish males	153 (50)	100	C-allele (64R) over-represented in endurance athletes compared to controls (Santiago et al., 2011).

AGT	rs699 (p.M235T)	Case-control	Professional cyclists, Olympic-class endurance runners and power athletes	Spanish males	163 (50)	119	No association with endurance. C-allele (235T) may favour power performance (Gomez-Gallego et al., 2009).
		Case-control	Professional cyclists, long-distance runners and handball players	Spanish males	60 (25)	400	No association with endurance (Alvarez et al., 2000).
AGTR1	rs12721277 (c.*82G>A)	Case-control	Professional cyclists, long-distance runners and handball players	Spanish males	60 (25)	400	No association with endurance (Alvarez et al., 2000).
AMPD1	rs17602729 (p.Q45X)	Case-control Quantitative $\dot{V}O_{2max}$ data	Professional cyclists and Olympic-class endurance runners	Spanish males	104 (50)	100	C-allele (45Q) over-represented in endurance athletes although do not have higher $\dot{V}O_{2max}$ (Rubio et al., 2005).
		Case-control	Professional cyclists, Olympic-class endurance runners and World class rowers	Spanish males	141 (50)	123	No association with endurance (Muniesa et al., 2010).
		Case-control Quantitative muscle power	Endurance, power and mixed athletes	Lithuanian males and females	204 (12)	260	TT genotype (45XX) absent from athlete group. T-allele under-represented in power athletes compared to controls. CC genotype associated with muscle power (Ginevičienė et al., 2014).
CKMM	rs8111989 (g.45809208 T>C)	Case-control	Professional cyclists and Olympic-class endurance runners	Spanish males	77 (50)	119	No association with endurance (Lucía et al., 2005).
		Case-control	Professional cyclists, Olympic-class endurance runners and World class rowers	Spanish males	141 (50)	123	No association with endurance (Muniesa et al., 2010).
GDF8	rs1805086 (p.K153R)	Case-control	Professional cyclists, Olympic-class endurance runners and World class rowers	Spanish males	141 (50)	123	No association with endurance (Muniesa et al., 2010).
HFE	rs1799945 (p.H63D)	Case-control	Professional road cyclists with hyperferritinemia	French males	77 (77)	254	G-allele (63D) over-represented in cyclists compared to controls (Deugnier et al., 2002).
		Case-control Quantitative $\dot{V}O_{2max}$ data	Professional cyclists and Olympic-class endurance runners	Spanish males	65 (50)	134	G-allele (63D) over-represented in endurance athletes although do not have higher $\dot{V}O_{2max}$ (Chicharro et al., 2004).
IL6	rs1800795 (c.-174C>G)	Case-control	Professional cyclists, Olympic-class endurance runners and power athletes	Spanish males	153 (50)	100	No association with endurance. GG genotype and G-allele over-represented in power athletes compared to controls or endurance athletes (Ruiz et al., 2010).

IL15RA	rs2228059 (p.N12T)	Case-control	Mixed endurance and sprint-power sports	European Australian males and females	308 (73: 43 endurance; 30 sprint-power)	258	A-allele (12N) over-represented in all cyclists compared to controls (Pistilli et al., 2011).
MtDNA	Haplogroup	Case-control	Professional cyclists, Olympic-class endurance runners and power athletes	Spanish males	153 (50)	478	V haplogroup over-represented in elite endurance athletes compared to controls (Nogales-Gadea et al., 2011).
NOS3	rs2070744 (c.-786C>T)	Case-control	Professional cyclists, Olympic-class endurance runners and power athletes	Spanish males	153 (50)	100	No association with endurance. TT genotype and T-allele over-represented in power athletes compared to controls or endurance athletes (Gómez-Gallego et al., 2009).
PER3	VNTR (54 bp repeat)	Case-control	Cyclists, runners and Ironman triathletes	South African males of European descent	532 (125)	96	PER3(5/5) over-represented in all athletes compared to controls (Kunorozva, Stephenson, Rae, & Roden, 2012).
PPARA	rs4253778 (c.2528G>C)	Case-control Quantitative muscle power	Endurance, power and mixed athletes	Lithuanian males and females	193 (12)	250	C-allele over-represented in all athletes compared to controls (Ginevičienė, Pranckevičienė, Milašius, & Kučinskas, 2010).
PPARD	rs2016520 (c.-87C>T)	Case-control	Endurance and power athletes from a range of sports	Russian males and females	1256 (108)	610	C-allele over-represented in endurance athletes (Ahmetov, Astratenkova, & Rogozkin, 2007)
PPARGC1A	rs8192678 (p.G482S)	Case-control Quantitative $\dot{V}O_{2max}$ data	Professional cyclists and Olympic-class endurance runners	Spanish males	104 (50)	164	G-allele (482G) predicts exceptional endurance capacity (Lucia et al., 2005).
		Case-control	Professional cyclists, Olympic-class endurance runners and World class rowers	Spanish males	141 (50)	123	No association with endurance (Muniesa et al., 2010).
		Case-control Quantitative muscle power	Endurance, power and mixed athletes	Lithuanian males and females	193 (12)	250	482S homozygotes had higher power performance (Ginevičienė, Pranckevičienė, Milašius, & Kučinskas, 2010).
TFAM	rs1937 (p.S12T)	Case-control Quantitative $\dot{V}O_{2max}$ data	Endurance and power athletes from a range of sports	Russian	1537 (109)	1113	C-allele (12T) over-represented in endurance athletes (Ahmetov, Popov, Missina, Vinogradova, & Rogozkin, 2010).
VEGFA	rs2010963 (c.-634C>G)	Case-control Quantitative $\dot{V}O_{2max}$ data	Endurance and power athletes from a range of sports	Russian males and females	670 (110)	1073	C-allele over-represented in endurance athletes (Ahmetov et al., 2008).

VEGFR2	rs1870377 (p.Q472H)	Case-control Quantitative $\dot{V}O_{2max}$ data	Endurance and power athletes from a range of sports	Russian males and females	471 (11)	603	A-allele (472Q) with endurance-related phenotypes (Ahmetov et al., 2009).

Table 1. Candidate gene association studies comparing cyclists to controls showing study characteristics and findings.

STUDY	PRIMARY DESIGN	PARTICIPANTS	
GENATHLETE	Candidate gene case-control multicentre study	~300	Endurance athletes with high $\dot{V}O_{2max}$
		~300	Untrained controls with low to average $\dot{V}O_{2max}$
RUSSIAN COHORT	Candidate gene case-control study involving 24 different athletic disciplines	1423	Russian endurance athletes of regional or national competitive standards
		1242	Russian controls
EAST AFRICAN COHORT	Candidate gene case-control study	291	Kenyan endurance athletes of national / international standard
		85	Kenyan controls
		76	Ethiopian endurance athletes from junior / senior national athletic teams
		315	Ethiopian controls
JAMAICAN AND USA COHORT	Candidate gene case-control study and GWAS	116	Jamaican sprint athletes of national/ international competitive standard
		311	Jamaican controls
		114	African-American sprint athletes of national / international competitive standard
		191	African-American controls
AUSTRALIAN COHORT	Candidate gene case-control study involving 14 different sports	429	Elite white athletes
		436	White controls
JAPANESE COHORT	Candidate gene case-control study and GWAS	717	Japanese athletes of national / international competitive standard including 381 track and field athletes, 166 swimmers and 170 Olympians from various sports
		814	Japanese controls
EUROPEAN AND ASIAN SWIMMING COHORT	Candidate gene case-control study	200	Caucasian swimmers of world-class status
		158	Japanese of national competitive standards
		649	Japanese controls
		168	Taiwanese swimmers of national / international competitive standards
		603	Taiwanese controls
SPANISH COHORT	Candidate gene case-control study	100	Spanish male endurance athletes of world-class status
		54	Spanish male rowers of world-class status
		108	All-time best Spanish Judo male athletes
		88	Swimmers of national level
		53	Power athletes of national / international competitive standards
		343	Spanish controls
ISRAELI COHORT	Candidate gene case-control study	74	Israeli endurance athletes of national / international competitive standard
		81	Power athletes of national / international competitive standard
		240	Israeli controls
CHINESE COHORT	Candidate gene case-control study	241	Chinese (HAN) endurance athletes
		504	Chinese (HAN) controls
POLISH COHORT	Candidate gene case-control study involving 20 different athletic disciplines	660	Polish athletes of national / international competitive standard
		684	Polish controls
LITHUANIAN (Kaunas) COHORT	Candidate gene association study involving 19 different athletic disciplines performing over 20 groups of phenotypic measurements	126	Strength-power athletes of regional / national / international standard including Olympic athletes
		84	Endurance athletes of regional / national / international standard including Olympic athletes
		197	Lithuanian controls

LITHUANIAN (Vilnius) COHORT	Candidate gene association study involving 15 different athletic disciplines performing 3 groups of phenotypic measurements	59	Endurance athletes of international / regional standard
		71	Strength and speed athletes of international / regional standard
		431	Mixed team sports athletes of international / regional standard
		260	Lithuanian controls

Table 2. Major study cohorts in genetics of elite performance (see Pitsiladis et al., 2013).