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ARTICLE

The Genetics of VO_2: What is the impact of endurance genes on VO_2 max in athletes?

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Endurance athletes typically develop a very high VO_2 max through training compared to nonendurance athletes. Training accounts for an average VO_2 max improvement of 14% amongst athletes (Keller et al., 2010). Previous studies have indicated that VO_2 max is also heavily influenced by genetics. Many studies that examine the genetic basis of VO_2 max fail to consider all the relevant genes together. This paper aims to combine this information and determine whether one gene is the most significant for endurance athletes looking to improve their VO_2 max. Thirteen research papers retrieved from the University of Toronto's online database were used along with reliable online sources to compile the information used in this review. The papers analyzed examined eight genes: NRF1, NFE2L2, ADRB2, ACE, ACSL1, ACTN3, PPARA and COL5A1. Of these, four were found to impact VO_2 max in endurance athletes (ACE, ACSL1, COL5A1, PPARA). The impact of these four genes ranged from 2% to 7%, suggesting a slight but notable implication. The ACTN3 gene was found to have an impact, but only in sprint and strength athletes. While the impact of individual genes was small, further studies need to examine the interaction effect of these genes on VO_2 max. Also, studies need to be more controlled in that they should have more variability in the participants and require control groups for the results of the studies to be reliable, accurate and applicable to everyone.

INTRODUCTION

Professional endurance athletes are capable of having a higher, more developed VO_2 max. VO_2 can be trained, and specific workouts can target this. Genetics can account for 50% of VO_2 max (Orysiak et al., 2013). So, then the question arises whether having a specific gene can be beneficial for an endurance athlete.

A gene is a hereditary unit made up of DNA that has instructions for a cell. Each gene codes for a protein or a function. VO_2 max is the maximum oxygen uptake of a person. At a person's maximum capacity, oxygen uptake plateaus and their aerobic system switches to anaerobic power production, meaning without oxygen. "VO_2 max reflects the limitation of oxidative metabolism of active muscle cells (peripheral limitation) as well as the capacity for oxygen delivery by the heart and the vascular system (central limitation)" (Hoppeler, 2018, p. 1). Between sedentary individuals, VO_2 max can vary greatly. Professional endurance athletes will develop a higher VO_2 max than sedentary individuals because of its' trainability. Their high levels of oxygen uptake indicate a more efficient cardiovascular system and use a high amount of oxygen during long-distance exercise. This efficiency helps to maintain glucose storage later used in the anaerobic system.

Professional male athletes can have a VO_2 max of 80 ml O2 min−1 kg−1, which is on the high end of collected VO_2 max data, and this value is about 15% lower for female professional athletes (Hoppeler, 2018). Endurance sports utilize type I slow-twitch fibres in muscles meaning the muscles use "oxygen in a more efficient manner during continuous muscle activity" (Lopez- Leon et al., 2015, p. 5). Examples of sports using type I slow-twitch muscle fibres are cycling, long-distance running, cross country skiing, swimming, and rowing. Additionally, VO_2 max is a factor that can be tested and measured. A method of measuring VO_2 max is by using a face mask to record the volume and gas concentration of an athlete's inspired and expired air while performing an exercise test where the intensity is steadily increasing (University of Virginia, 2020).

Many of the studies currently available on VO_2 max examine the influence of a single gene. These studies fail to consider the potential combined effect of multiple genes on VO_2 max. Many athletes train hard to improve their VO_2 max, so it would be important to know how close their current VO_2 max is to their plateau based on their genetics. This paper will aim to determine if particular genes influence an endurance athlete's VO_2 max.

METHOD

This research paper combines information from several different studies downloaded from the University of Toronto's online database. Keywords used in the search were: endurance, VO_2 max, genes and training response. Inclusion criteria for a paper were: relevance, English language, human subjects, and ethical guideline adherence. The 24 initial papers retrieved were reviewed by reading their abstracts and examining the figures. After review, 13 did not meet the criteria and were excluded leaving 11 papers for further analyses (see Appendix A for papers used). It has been noted that most of the papers used have a publishing bias in that they were given grants for the research, but these were for financial purposes in the study and should not affect the results obtained in those studies.

RESULTS

When analyzing results from the research papers used, a total of 8 genes were identified, along with one paper identifying mitochondrial gene clusters. Most of these genes were found to have only a small impact on VO_2 max. Figure 1 shows the results of the combined studies and the limited effect of these genes.

In the analyzed articles, individuals that were identified as having the gene being studied were tested for their change in VO_2 max. They had the potential to develop this change in their VO_2 max through the prescribed training. This is defined as the training response (Figure 1). A study by Keller et al. (2010) "reported an average 14% improvement in … VO_2 max in response to 6 wk of endurance training". The COL5A1 gene had a 7% training response indicating that it is the gene with the biggest impact on an athlete's VO_2 max. Figure 1 shows that the impact of the genes on VO_2 max is very small. Four genes (ACTN3, ADRB2, NFE2L2, NRF1) have no impact on VO_2 max, and the other four genes (ACE, ACSL1, COL5A1, PPARA) have an impact ranging from 2-7%, which is very small. Though 7% training response should not be neglected in an athlete and is considered statistically significant, it is a small factor compared to the whole 50% heredity of VO_2 max. Additionally, the ACE gene is the most common and studied gene in this area of research as it is the first gene identified to have a link to endurance sports (Gomez-Gallego, 2008). As seen in Figure 1, it was found that ACE had a 2.1% impact on VO_2 max, but this is controversial as numerous studies have found no impact. To better understand these results, Table 1 shows the roles of the four genes found to influence VO_2 max in humans (Table 1).

A study by Posthumus et al. (2011) found that the least flexible athletes had more optimal endurance performance and, therefore, a lower steady-state VO_2 (lower oxygen uptake plateau) related to the T allele of the COL5A1 gene. For the PPARA gene, those with the G allele had a higher endurance ability than those with the C allele (Lopez-Leon et al., 2015). Additionally, it can be noted that though Figure 1 shows no impact on VO_2 max with the ACTN3 gene it is more related to strength than endurance and could affect VO_2 max when testing sprint athletes (Wessner et al., 2016). This is because ACTN3 codes for a protein found in fast-twitch muscle fibres, and endurance athletes have been found to lack the genotype coding for fast-twitch fibres (NIH).

DISCUSSION AND EVALUATION

This study aimed to investigate whether there was one gene that showed a significant impact and that would be greatly beneficial to endurance athletes regarding their VO_2 max; however, this was not found. Instead, eight genes were identified as having the potential to be related to VO_2 max, and only four of them had an impact. Since many genes influence VO_2 max, it is hard to pinpoint one gene with a great impact or to study all the genes together.

Individually they all have small impacts; combined, they could have a greater influence on an athlete's VO_2 max. The genes ACE, ACSL1, COL5A1 and PPARA were found to have a small impact. The effect of these genes ranges from 2-7%, meaning that their effect is small compared to the effect that training can have on improvements for VO_2. What has not been noted above in the results is that in addition to genes, a study by Stepto et al. (2009) found a correlation between mitochondrial gene clusters and VO_2 max as well as fat and carbohydrate oxidation gene clusters with VO_2 max. This makes sense as endurance training is performed in the anaerobic state, using carbohydrates as fuel instead of glucose,

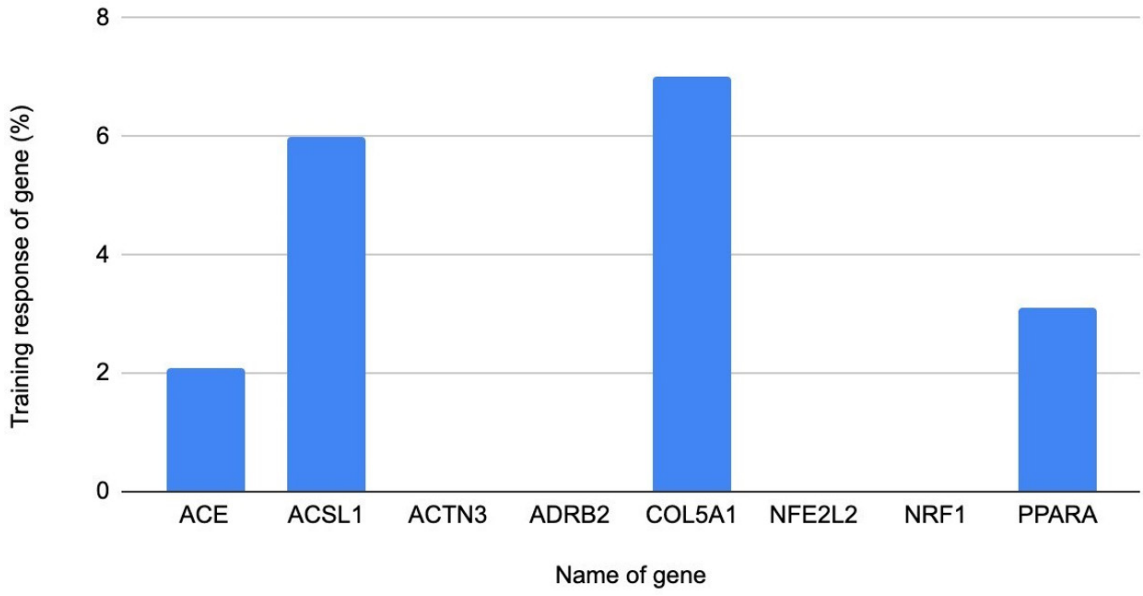

Figure 1: Impact of each gene on VO_2 max as identified by the training response

hence showing its' positive long-term effect on the up regulation of fat oxidative genes (Stepto et al., 2009). Another factor contributing to the high VO_2 max of an endurance athlete is their muscular composition which is also influenced by genetics. Type I muscle fibres (slow twitch) have a "greater mitochondrial and capillary density" (Sarpeshkar and Bentley, 2010, p. 479) than type II muscle fibres (fast-twitch). Compared to strength athletes who have more fast-twitch fibres, endurance athletes display greater slow-twitch fibres and myoglobin, which contributes to their higher VO_2 max.

When combining the 11 research papers used from the University of Toronto, in total, there were 512 male participants, 46 female participants, 302 participants where the gender was not specified, and 269 control individuals for a total of 1129 participants across all studies. Three studies also used data from the HERITAGE study. This was a study assessing the role of genes

in a 20-week exercise program among families. The study had 230 male participants and 243 female participants. Additionally, two research papers did not conduct studies but rather did a literature review using databases. The lack of female participants presents the first limitation to this study as females and males have different physiological characteristics that could influence the results. Furthermore, only 3 of the 9 papers that conducted studies with humans had control groups. The absence of control groups makes it: difficult to compare the results obtained, less re-

Table 1: Functions of genes found to effect VO_2 max

Gene	Function	Location and Alleles
ACE	"contributes to blood pressure, fluid and salt balance" (Williams et al., 2016, p. 103)	located on chromosome 17, has an Insertion (I) or Deletion (D) allele, the Insertion allele relates more to endurance
ACSL1	required for the activation and transport of long-chain fatty acids into mitochondria (Ghosh et al., 2013) and for converting free long-chain fatty acids into fatty acyl-CoA esters (GeneCards)	located on chromosome 4, A and G alleles
COL5A1	"encodes the pro-α1 chain of type V collagen" (Jones et al., 2016, p. 118) (collagen is a protein that strengthens tissues)	located on chromosome 9, T and C alleles, the T allele is associated with endurance
PPARA	"regulates liver, heart and skeletal muscle lipid metabolism, glucose homeostasis" (Jones et al., 2016, p. 118) and more	located on chromosome 22, C and G alleles, the G allele is associated with endurance

liable, challenging to analyze the responses to interventions, and difficult to apply the results to the general population. There is also a lack of variability in the participants: notably, all studies examined people of Caucasian descent, which means the results cannot be applied to everyone. Many studies had a small sample size making the results less significant and less reliable. Also, studies tended to not look at all the variants of a gene but chose to focus on one allele, meaning that possible important results were excluded. External factors and the epigenetics of participants were not considered; however, these have significant effects on a person's behaviours and genetics, making the results less reliable again. Lastly, three studies used data from the HERITAGE study; while they may have looked at different aspects, the results lack variability as the same data was used. All these limitations mentioned result in a lack of statistical power or significance. The studies also had strengths in that their methodologies were well thought out and were carried out in a precise manner, and most studies offer a pertinent discussion of their results even when no impact was found.

This present study has the limitation that it was difficult to find research that pertained to the subject, meaning that only one study was found for each gene. The COL5A1 gene and the ACE gene are exceptions as there were 2 studies and 3 studies, respectively, addressed these genes. Future studies should address these limitations, notably having more variability in the

participants and having control groups. Also, since each gene has such a small impact on VO_2 max, a combination of these genes should be tested in athletes in a study to determine their combined effect in comparison to the effect of training. Though this present study only examined endurance sports and athletes, sprint and strength athletes could also be studied either for their VO_2 max or for genes that are common in athletes of those disciplines.

Findings such as those presented in this paper are important and relevant for endurance athletes and coaches. They can be used to determine whether VO_2 max training should be a priority or not for the athlete. Once further studies about this topic are done, if an athlete knows their genomic profile, they can determine whether VO_2 max is an athletic strength or a weakness which would greatly help their training and racing style.

REFERENCES

ACSL1 Gene - GeneCards | ACSL1 Protein | ACSL1 Antibody. (n.d.). Www.genecards.org. http://www.genecards.org/cgi-bin/carddisp.pl?gene=ACSL1#:~:text=ACSL1 Belli, T., Crisp, A., & Verlengia, R. (2017). Greater muscle damage in athletes with ACTN3 R577X

(RS1815739) gene polymorphism after an ultra-endurance race: a pilot study. *Biology of Sport*, 34(2), 105–110. Biology of Sport, University of Toronto. https://doi.org/10.5114/biolsport.2017.64583

Brown, J. C., Miller, C.-J., Posthumus, M., Schwellnus, M. P., & Collins, M. (2011). The COL5A1 Gene, Ultra-Marathon Running Performance, and Range of Motion. *International Journal of Sports Physiology and Performance*, 6(4), 485–496. https://doi.org/10.1123/ijspp.6.4.485

Genetics Home Reference. (2018, January). Is athletic performance determined by genetics? *Genetics Home Reference; NIH U.S. National Library of Medicine*. https://ghr.nlm.nih.gov/primer/traits/athleticperformance

Ghosh, S., Vivar, J. C., Sarzynski, M. A., Sung, Y. J., Timmons, J. A., Bouchard, C., & Rankinen, T. (2013). Integrative pathway analysis of a genome-wide association study of V̇o2max response to exercise training. Journal of Applied Physiology, 115(9), 1343–1359. University of Toronto. https://doi.org/10.1152/japplphysiol.01487.2012 Gómez-Gallego, F., Santiago, C., González-Freire, M., Muniesa, C., Fernández del Valle, M., Pérez, M., Foster, C., & Lucia, A. (2008). Endurance Performance: Genes or Gene Combinations? *International Journal of Sports Medicine,* 30(01), 66–72. University of Toronto. https://doi.org/10.1055/s-2008-1038677

Hoppeler, H. (2018). Deciphering V̇O2,max: limits of the genetic approach. Journal of Experimental Biology, 221(21). https://doi.org/10.1242/jeb.164327

Jones, N., Kiely, J., Suraci, B., Collins, D., de Lorenzo, D., Pickering, C., & Grimaldi, K. (2016). A genetic-based algorithm for personalized resistance-training. *Biology of Sport*, 33(2), 117–126. https://doi.org/10.5604/20831862.1198210

Keller, P., Vollaard, N. B. J., Gustafsson, T., Gallagher, I. J., Sundberg, C. J., Rankinen, T., Britton, S. L., Bouchard, C., Koch, L. G., & Timmons, J. A. (2010). A transcriptional map of the impact of endurance exercise training on skeletal muscle phenotype. Journal of Applied Physiology, 110(1), 46–59. University of Toronto. https://doi.org/10.1152/japplphysiol.00634.2010

Lopez-Leon, S., Tuvblad, C., & Forero, D. (2015). Sports Genetics: the PPARA Gene and Athletes' High Ability in Endurance Sports. A Systematic Review and Meta-Analysis. *Biology of Sport*, 33(1), 3–6. University of Toronto. https://doi.org/10.5604/20831862.1180170

Mandal, A. (2019, May 22). *What are Genes?* News-Medical.net; News Medical Life Sciences. http://www.news-medical.net/life-sciences/What-are-Genes.aspx

Orysiak, J., Zmijewski, P., Klusiewicz, A., Kaliszewski, P., Malczewska-Lenczowska, J.,

Gajewski, J., & Pokrywka, A. (2013). THE ASSOCIATION BETWEEN ACE GENE VARIATION AND AEROBIC CAPACITY IN WINTER ENDURANCE DISCIPLINES. *Biology of Sport*, 30(4), 249–253. University of Toronto. https://doi.org/10.5604/20831862.1077549

POSTHUMUS, M., SCHWELLNUS, M. P., & COLLINS, M. (2011). The COL5A1 Gene. *Medicine & Science in Sports & Exercise*, 43(4), 584–589. University of Toronto. https:// doi.org/10.1249/mss.0b013e3181f34f4d

Sarpeshkar, V., & Bentley, D. J. (2010). Adrenergic-β 2 receptor polymorphism and athletic performance. Journal of Human Genetics, 55(8), 479–485. Nature. https://doi.org/10.1038/jhg.2010.42

STEPTO, N. K., COFFEY, V. G., CAREY, A. L., PONNAMPALAM, A. P., CANNY, B. J., POWELL, D., & HAWLEY, J. A. (2009). Global Gene Expression in Skeletal Muscle from Well-Trained Strength and Endurance Athletes. *Medicine & Science in Sports & Exercise*, 41(3), 546–565. University of Toronto. https://doi.org/10.1249/ mss.0b013e31818c6be9

Timmons, J. A., Knudsen, S., Rankinen, T., Koch, L. G., Sarzynski, M., Jensen, T., Keller, P., Scheele, C., Vollaard, N. B. J., Nielsen, S., Åkerström, T., MacDougald, O. A., Jansson, E., Greenhaff, P. L., Tarnopolsky, M. A., van Loon, L. J. C., Pedersen, B. K., Sundberg, C. J., Wahlestedt, C., & Britton, S. L. (2010). Using molecular classification to predict gains in maximal aerobic capacity following endurance exercise training in humans. *Journal of Applied Physiology*, 108(6), 1487–1496. University of Toronto. https://doi.org/10.1152/japplphysiol.01295.2009

VO_2 Max Testing. (2020). *Exercise Physiology Core Laboratory*; University of Virginia. http://med.virginia.edu/exercise-physiology-core-laboratory/fitness-assessment-forcomm unity-members/vo2-max-testing/

Wessner, B., & Stuparits, P. (2016). Genetic polymorphisms in alpha-actinin 3 and adrenoceptor beta genes in Austrian elite athletes and healthy controls. *Swiss Sports & Exercise Medicine*, 64(4), 13–19. University of Toronto. https://doi.org/10.34045/ssem/2016/21

Williams, C. J., Williams, M. G., Eynon, N., Ashton, K. J., Little, J. P., Wisloff, U., & Coombes, J. S. (2016). Genes to predict VO_2max trainability: a systematic review. BMC Genomics, 18(Suppl 8), 81–110. University of Toronto. https://doi.org/10.1186/s12864-017-4192-6

Appendix

Appendix A: Data from 11 research papers retrieved from the University of Toronto's database

Name of paper, author, publishing year	Participants (number, type)	Type of sport of athletes studied	Gene(s) studied	Method of data collection	Grant?
The COL51A1 Gene, Ultra-Marathon Running Performance, and Range of Motion (Brown et al., 2011)	52 male and 20 female runners recruited from the 56km Two Oceans ultramarathon race	Running (ultramarathon)	COL5A1	DNA extracted from 5 mL of venous blood obtained by venipuncture of the forearm vein	Yes 1
Integrative pathway analysis of a genome-wide association study of VO2max response to exercise training (Ghosh et al., 2013)	Data from HERITAGE study with 230 male and 243 female Caucasians between 17 and 65 years old	Sedentary at baseline, followed an exercise protocol on cycle ergometers	Pathway analysis- example of gene: ACSL1	Genomic DNA prepared from immortalized lymphoblastoid cell lines using a DNA extraction kit	Yes 1
Endurance Performance: Genes or Gene Combinations? (Gomez-Gallego et al., 2008)	46 professional male road cyclists, 46 sedentary male controls, all Spanish (Caucasian)	Road Cycling	ACE, ACTN3	Respiratory gas exchange measured using a breath-by-breath system, Genomic DNA extracted from peripheral EDTA treated anti-coagulated blood	No 3
A transcriptional map of the impact of endurance exercise training on skeletal muscle phenotype (Keller et al., 2010)	24 young sedentary healthy Caucasian men and data from HERITAGE study with 473 subjects	n/a- trained on cycle ergometer	n/a- various single-nucleotide polymorphisms studies	Physiological measurements and vastus lateralis muscle biopsies	Yes 2
Sports genetics: the PPARA gene and athletes' high ability in endurance sports. A systematic review and meta-analysis (Lopez-Leon et al., 2015)	Meta analysis of 5 studies with a total of 760 endurance athletes and 1792 controls	Sports in all 5 studies: rowing, marathon, biathlon, triathlon, cross country skiing, swimming, skating, road cycling	PPARA	Research published on PubMed up to April 2015 studying the association between the PPARA G/C polymorphism and endurance sports	Yes 1

Appendix

Appendix A: Data from 11 research papers retrieved from the University of Toronto's database (Cont'd)

The Association between ACE Gene Variation and Aerobic Capacity in Winter Endurance Disciplines (Orysiak et al., 2013)	26 female and 40 male well trained athletes between 15 and 21 years old	48 cross country skiers, 8 biathlon athletes, 10 Nordic combined athletes	ACE	DNA extracted from 5 mL of venous blood taken from volunteers and collected in EDTA tubes and stored at -20°C	Yes 2
The COL5A1 Gene: A Novel Marker of Endurance Running Performance (Posthumus et al., 2011)	313 male Caucasians who finished the 2006 or 2007 226-km South African Ironman triathlons	Ironman triathlon: 3.8 km swim, 180km bike, 42.2km run	COL5A1	DNA extracted from 4.5 mL of venous blood obtained by venipuncture of a forearm vein	Yes 2
Global Gene Expression in Skeletal Muscle from Well-Trained Strength and Endurance Athletes (Stepto et al., 2009)	20 male participants- 7 endurance trained, 6 strength trained, 7 control	Cycling for the endurance trained, powerlifting for the strength trained	263 genes found in participants - mitochondrial gene clusters were studied	Resting skeletal muscle samples obtained from the vastus lateralis	Yes 2
Using molecular classification to predict gains in maximal aerobic capacity following endurance exercise training in humans (Timmons et al., 2010)	24 young sedentary healthy Caucasian men, 17 young active Caucasian subjects and data from HERITAGE study with 473 subjects	Trained on cycle ergometers	n/a- molecular profile created and many genes examined	Physiological measurements and vastus lateralis muscle biopsies	Yes 1
Genetic polymorphisms in alpha-actinin 3 and adrenoceptor beta genes in Austrian elite athletes and healthy controls (Wessner et al., 2016)	285 athletes and 216 control both female and male genders, Caucasian, aged 18-83 years old	56 power athletes: sprint and jump 86 endurance athletes: running, cycling, triathlon 143 team sport athletes: soccer, handball	ACTN3, ADRB1, ADRB2, ADRB3	Genomic DNA from saliva, polymerase chain reation	Yes 2
Genes to predict VO2max trainability: a systematic review (Williams et al., 2016)	n/a- review paper from research found in four databases, but primarily Caucasian participants	n/a	97 genes identified in papers used ie: NRF1, ADRB2, APOE, ACE	Peer-reviewed research papers published up until October 2016 from four databases	Yes 2

1: but there is no direct statement regarding conflict of interest

2: states there is no conflict of interests and/or endorsement

3: no statement regarding grants

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I'm Natasha Badertscher, a recent high school graduate from Toronto. I'm a competitive cyclist and I race on the road and the track. My journey as an athlete piqued my interest in research and information about the human body and mind. I will be studying psychology in university. Furthermore, I'm passionate about encouraging youth to stay in sport.