# Mapping Robust Genetic Variants Associated with Exercise Responses

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Key words
trainability, aerobic exercise, exercise genetics, resistance exercise, SNPs, genetic variants

**accepted** 01.06.2020

Bibliography
**DOI** https://doi.org/10.1055/a-1198-5496
Published online: 2020
Int J Sports Med

ISSN 0172-4622

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**ABSTRACT**

This review summarised robust and consistent genetic variants associated with aerobic-related and resistance-related phenotypes. In total we highlight 12 SNPs and 7 SNPs that are robustly associated with variance in aerobic-related and resistance-related phenotypes respectively. To date, there is very little literature ascribed to understanding the interplay between genes and environmental factors and the development of physiological traits. We discuss future directions, including large-scale exercise studies to elucidate the functional relevance of the discovered genomic markers. This approach will allow more rigour and reproducible research in the field of exercise genomics.

## Introduction

Both aerobic and strength exercise training lower the incidence of many chronic diseases via a number of mechanisms, including increased skeletal muscle mitochondrial function [1], modulation of the sympathetic nervous and immune systems, and optimization of the neuroendocrine system [2]. These mechanisms act as buffers against chronic diseases, minimizing inflammatory state, and enhancing neuroplasticity and growth factor expression [3]. However, large inter-individual differences exist in the physiological responses to any given exercise training (also called "trainability") [4, 5], and recently new statistical methods have been developed to properly isolate individual responses from random error [6]. Large trainability has been observed in many physical fitness parameters [7], including maximal oxygen uptake ($VO_2$max) [8, 9], resting heart rate [9], exercise heart rate [9], aerobic threshold [10], anaerobic threshold [9], resting muscle glycogen content, muscle enzyme activity [11], as well as muscle mass and strength [12, 13].

The heritable component of trainability is large, with genetics explaining 47 % of the variance in $VO_2$ peak trainability, and around 52 % in resistance variability [14]. The contribution of familial factors (genetics and environment) to trainability was demonstrated in the seminal HERITAGE family study [15]. This study indicated that $VO_2$max was more variable between families than within families at baseline [16], and in response to exercise training [17], thus suggesting that DNA sequence variations could modulate exercise responses [4, 18]. Pinpointing the responsible gene variants could illuminate the fundamental mechanisms driving this heterogeneity in response to exercise training [18].

The genetic contribution to trainability has been investigated by two different approaches: candidate genes and genome-wide association (GWAS) study. The GWAS approach involves scanning

several hundred thousand (currently up to 5 million) DNA markers across the human genome to find genetic variations associated with a particular trait. One of the advantages of the GWAS approach is that it is unbiased and hypothesis-free. In contrast, candidate gene studies require knowledge of the trait of interest and is particularly useful to validate the functional impact of gene loci such as those identified by GWAS [19]. GWAS have demonstrated that trainability is polygenic (i. e., influenced by many genetic variants), and that people harbouring the same genotypes in specific gene variants respond more similarly to exercise training than people harbouring different genotypes [20–23]. These variants may modulate gene expression that is essential to the molecular adaptation to exercise training, since molecular processes mediate metabolism, angiogenesis, cardiac and skeletal myofibre hypertrophy, and other processes that lead to better fitness [24].

While many SNPs have been associated with exercise response and trainability. The vast majority of the genes previously identified have not been replicated [25]. Replication in an independent cohort is important as it increases the likelihood that results are true and reduces the number of false positives [26, 27]. In this review we summarised SNPs associated with both resistance and aerobic trainability and have been replicated in two independent cohorts. In addition, we have screened these SNPs with the goal of identifying SNPs at trainability-associated loci that may have functional relevance. Further, we discussed future directions of performing large-scale exercise studies to elucidate the functional relevance of the discovered genomic markers. This approach will allow more rigour and reproducible research in the field of exercise genomics.

## Materials and Methods

To provide a robust and comprehensive narrative review, a semi-structured search was performed (July 2019) to identify all studies relating to genetic variants and exercise trainability. Three electronic databases (PUBMED, MEDLINE and SCOPUS) were used to identify relevant articles using the following keywords “genes”, “genome”, “exercise”, “physical activity”, “aerobic capacity”, “resistance”, “strength”, “power”. We excluded studies where the sole focus was on populations with a diagnosed medical condition such type 2 diabetes mellitus, any inflammatory conditions, and cardiovascular disease. Articles were separated in two categories: genetic variants associated with either aerobic or resistance trainability (▶ **Tables 1** and ▶ **2**). This review was conducted in accordance with the IJSM’s ethical standards of the journal [28]

Finally, we selected SNPs that were classified as robust and separated them according to whether they were related to the aerobic trainability or resistance trainability. We chose this criteria as it reflects the reliability of the findings and increases the likelihood that there is true association of the SNP with trainability [27]. It also allows us to identify and summarise SNPs with biological relevance which is useful for researchers to ‘select’ candidate SNPs to identify causality and purpose of gene [29].

SNPs were considered robust if:

1) Consistent association with a given phenotype in at least *two independent* cohorts.
2) SNPs were shown to have functional relevance in an animal model or cell culture, with gene expression/DNA methylation Quantitative Trait Loci (QTLs) analysis or network, and enrichment analysis.

### Aerobic Trainability

Twin and family studies indicate that ~22–57 % of aerobic fitness variability between individuals can be explained by genetics and therefore plays an important role in the range of aerobic phenotypes observed in a population [30]. Here, we briefly describe some of the robust SNPs that have been associated with aerobic trainability, which means they were replicated in at least 2 independent cohorts and were shown to have functional relevance.

A bioinformatic analysis study conducted by Ghosh et al. found that the greatest number of SNPs were annotated to the PPAR signalling pathway suggesting its importance in $VO_{2max}$ trainability [31]. As such the most widely studied genes within this pathway are the peroxisome proliferator-activated receptors (*PPARA, PPARG,* and *PPARD*) and their transcriptional coactivators (*PPARGC1A* and *PPARGC1B*). These genes have been linked to multiple aerobic phenotypes, including muscle morphology, aerobic capacity and endurance performance [32, 33]. *PPARD* is expressed predominantly in adipocytes and skeletal muscle where it promotes fatty acid oxidation [34]. In the HERITAGE family study, the rs2016520 SNP (C allele) located in *PPARD* was associated with reduced $VO_{2max}$ and maximal power output after a 20 week endurance training intervention in African-Americans but not in Caucasians [35]. *In vitro* and animal studies show that the minor allele (C allele) in this SNP (rs2016520) results in higher *PPARD* transcriptional activity, which in turn promotes lipid accumulation and the alters normal regulation of lipid uptake and storage [34, 36, 37]. In a European cohort it was shown that the *PPARD* rs2267668 SNP was associated with $VO_{2peak}$ and anaerobic threshold after a 9-month lifestyle intervention [38]. They then confirmed that in human primary cell lines that those carrying the minor allele at rs2267668 (G allele) were associated with lower mitochondrial activity, demonstrating a potential functional effect [38]. Taken together, *PPARD* locus may play a role in aerobic trainability, but larger cohorts of different ancestries and, more in depth functional studies to determine causal SNP are needed to confirm this.

The transcriptional co-activator *PPARGC1A* interacts with *PPARD* and regulates mitochondrial biogenesis, angiogenesis, lipolysis and adipogenesis [39]. Four candidate gene studies, predominantly in men, found consistent associations of rs8192678 within *PPARGC1A* and aerobic capacity in Europeans [38, 40–42]. While in the Han Chinese cohort another nearby SNP (rs6821591) was associated with $VO_{2max}$ specifically, the G allele was associated with increased $VO_{2max}$ compared to those carrying the A allele [43]. Work conducted in a Han Chinese cohort found that the *PPARGC1A* rs6821591 SNP had functional significance as gene expression was altered and this was dependent on genotype (A v G allele) with the G allele displaying increased PGC-1α gene expression [44]. Overexpression of PGC-1α in an animal model showed increased Type 1 fibres in muscles that are normally Type II fibre type dense and this induced increases in resistance to fatigue, inferring increased aerobic capacity [45]. These population-specific results indicate that it is the

▶ **Table 1** Gene variants associated with aerobic trainability.

| Author, Date | Sample Size | Sex (% Males) | Age | Ancestry/Country / ethnicity | Chromosome | Annotated gene | Variant | Genotype and training response (+/−/0) | Intervention (if any)/exercise | Duration | Type of study |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Alves (2009)** [92] | N = 83 | Males only | 20–35 yrs | Brazil | 17<br>1 | *ACE*<br>*ATG* | rs4340<br>rs699 | ACE (0) $VO_{2max}$<br>TT (+) LVM | Moderate intensity endurance training | 3 days/ week<br>16 weeks | Candidate Gene |
| **Bouchard 2011** [23] | N = 742 | Males (N/A) and Females | 17–65 yrs | HERITAGE study Caucasian and African-American U.S.A | 4<br>6<br>9<br>3<br>9<br>3<br>1<br>1<br>20<br>11<br>14<br>15<br>11<br>14<br>2<br>4<br>11<br>3<br>22<br>11<br>6 | *ACSL1*<br>*PRDM1*<br>*GRIN3A*<br>*KCNH8*<br>*C9orf27*<br>*ZIC4*<br>*CAMTA1*<br>*RGS18*<br>*BIRC7*<br>*DBX1*<br>*DAAM1*<br>*NDN*<br>*CXCR5*<br>*TTC6*<br>*LOC400950*<br>*LOC100289626*<br>*LOC100130460*<br>*NLGN1*<br>*MN1*<br>*CD44*<br>*ENPP3* | rs6552828<br>rs10499043<br>rs1535628<br>rs4973706<br>rs12115454<br>rs11715829<br>rs884736<br>rs10921078<br>rs6090314<br>rs10500872<br>rs1956197<br>rs824205<br>rs7933007<br>rs12896790<br>rs4952535<br>rs2053896<br>rs2198009<br>rs2030398<br>rs738353<br>rs353625<br>rs10452621 | (+) VO2max | Endurance training Moderate: at 55% HR first two weeks and intense: last 6 weeks 75% HR | 20 weeks | GWAS |
| **Dionne (1991)** [93] | Males N = 46 | Males only | 17–29 yrs | Canada, USA | Mitochondria | *MTND2*<br>*MTND5* | | MTN2 (-) $VO_{2max}$<br>MTND5 (+) $VO_{2max}$ | Endurance training at 85% of HRR | 3–5 days/ week<br>20 weeks | Candidate gene |
| **Hautala et al. 2007** [35] | N = 478 | Males (48.3%) and Females | 17–65 yrs | HERITAGE study Caucasian and African-American Canada, U.S.A | 22 | *PPARD* | rs2016520<br>rs2076167 | African American only rs2016520 CC (-) $VO_{2max,}$ PPO<br>rs2076167 (0) | Endurance training moderate 55% of VO2 and absolute 75% of VO2 intensity | 20 weeks | Candidate gene |
| **He et al. 2008** [94] | N = 181 | Males only | 19 ± 1 | Han Chinese | 7<br>15 | *NRF-1*<br>*NRF-1*<br>*NRF-2* | rs2402970<br>rs6949152<br>rs6949152 | rs2402970 CC (+) VT, RE<br>rs6949152 AA (+) VT, RE<br>rs6949152 AA (+) VO2max | Endurance training 95% to 105% ventilatory threshold | 18 weeks | Candidate gene |

▶ **Table 1** Continued.

| Author, Date | Sample Size | Sex (% Males) | Age | Ancestry/Country / ethnicity | Chromosome | Annotated gene | Variant | Genotype and training response (+/−/0) | Intervention (if any)/exercise | Dura-tion | Type of study |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **He et al. 2006** [95] | N = 181 | Males only | 19 ± 1 | Han Chinese | 11 | *HBB* | rs10768683 | C (+) RE | Endurance training 95 % to 105 % ventilatory threshold | 18 weeks | Candidate gene |
| **He et al. 2007** [96] | N = 181 | Males only | 19 ± 1 | Han Chinese | 15<br>15<br>15 | *NRF-2*<br>*NRF-2*<br>*NRF-2* | rs12594956<br>rs8031031<br>rs7181866 | ATG haplotype (+) RE | Endurance training 95 % to 105 % ventilatory threshold | 18 weeks | Candidate gene |
| **He et al. 2008** [43] | N = 181 | Males only | 19 ± 1 | Han Chinese | 4<br>4<br>4 | *PPARGC1A*<br>*PPARGC1A*<br>*PPARGC1A* | rs17847357<br>rs8192678<br>rs6821591 | rs17847357,<br>rs8192678<br>(0) VO2max<br>rs6821591 G<br>(+) VO2max | Endurance training High intensity 95 % to 105 % HR | 18 weeks | Candidate gene |
| **He et al. 2010** [97] | N = 181 | Males only | 19 ± 1 | Han Chinese | 4<br>4<br>4<br>2<br>9 | *PPP3CA*<br>*PPP3CA*<br>*PPP3CA*<br>*PPP3R1*<br>*PPP3R2* | rs2850965<br>rs3804423<br>rs3804358<br>rs4671887<br>rs3739723 | G (+) VO2max<br>G (+) VO2max<br>G (+) VO2max<br>A (+) VO2max<br>A (+) RE | Aerobic endurance 95 % to 105 % of ventilatory threshold | 18 weeks | Candidate gene |
| **He et al. 2010** [98] | N = 181 | Males only | 19 ± 1 | Han Chinese | 8<br>8<br>8<br>8<br>8 | *PPP3CC*<br>*PPP3CC*<br>*PPP3CC*<br>*PPP3CC*<br>*PPP3CC* | rs1879793<br>rs1075534<br>rs7430<br>rs2461483<br>rs10108011 | CC (+) SV<br>AA (+) SV, CO<br>GG (+) SV<br>CC (+) SV<br>GG (+) SV | Aerobic endurance 95 % to 105 % of ventilatory threshold | 18 weeks | Candidate gene |
| **Leon et al. 2004** [99] | N = 766 | Males (43 %) and Females | 17–65 yrs | HERITAGE study Caucasian and African-American U.S.A | 19 | *APOE* | E2, E3, E4 | (0)VO2max | Endurance training Moderate: at 55 % HR first two weeks and intense: last 6 weeks 75 % HR | 20 weeks | Candidate Gene |
| **McKenzie 2011** [22] | N = 109 | Males (46.7 %) and Females | 50–75 yrs | Caucasian U.S.A | 14 | *AKT1* | rs1130214 | Men:<br>GG (+) VO2max<br>Females:<br>(0) | Aerobic training moderate 50–70 % | 24 weeks | Candidate gene |
| **McPhee et al 2011** [100] | N = 58 | Females only | Age 18–37 yrs | Caucasian UK | 14 | *HIF1A* | rs11549465 | T (+) VO2max | Aerobic 75–90 % of HRmax | 6 weeks | Candidate gene |
| **Pickering et al. 2018** [42] | N = 42 | Males only | 16–19 yrs | European (UK) | 4<br>4<br>4<br>4<br>4 | *PPARGC1A*<br>*VEGF*<br>*ADBR2*<br>*ADBR2*<br>*CRP* | rs8192678<br>rs2010963<br>rs1042713<br>rs1042714<br>1205 | Endurance genotype (+) Yo-Yo Test | Aerobic training moderate to intense | 8 weeks | Candidate gene |

▶ **Table 1** Continued.

| Author, Date | Sample Size | Sex (% Males) | Age | Ancestry/Country / ethnicity | Chromosome | Annotated gene | Variant | Genotype and training response (+/−/0) | Intervention (if any)/exercise | Duration | Type of study |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Prior et al. 2003** [101] | N = 233 | Males (39.3 %) and Females | 50–75 yrs | Caucasian and African-American U.S.A | 14 | *HIF1A* | rs28708675 rs11549465 | African American cohort: rs28708675 AA (+) VO2max Caucasian cohort: rs11549465 CC (+) VO2max | Aerobic training moderate 50–70 % | 24 weeks | Candidate gene |
| **Prior et al. 2006** [102] | N = 146 | Males (42 %) and Females | 50–75 yrs | Caucasian and African-American U.S.A | 6 | *VEGF* | rs699947 rs1570360 rs2010963 | AAG & CGC haplotypes (+) VO2max | Aerobic training moderate 50–70 % | 24 weeks | Candidate gene |
| **Rankinen et al. 2000** [103] | N = 472 | Males (49 %) and Females | Age 17–65 yrs | HERITAGE study Caucasian U.S.A | 1 | *ATP1A2* | Polymorphisms at exon 1 and 21–22 | 2α haplotype (+) VO2max and PP | Endurance training Moderate: at 55 % HR first two weeks and intense: last 6 weeks 75 % HR | 20 weeks | Candidate Gene |
| **Rankinen et al. 2000** [104] | N = 472 | Males (48.7 %) and females | Age 17–65 yrs | HERITAGE study Caucasian U.S.A | 17 1 | *ACE* *ATG* | rs4340 rs699 | Males: ACE I/D (0) ATG M (+) reduced diastolic blood pressure. Females: ACE I/D (0) ATG M/T (0) | Endurance training Moderate: at 55 % HR first two weeks and intense: last 6 weeks 75 % HR | 20 weeks | Candidate Gene |
| **Rico-Sanz et al. 2003** [105] | N = 779 | Males (N/A) and Females | Age 17–65 yrs | HERITAGE study Caucasian and African-American U.S.A | 1 | *AMPD1* | rs17602729 | TT (-) VO2max | Endurance training Moderate: at 55 % HR first two weeks and intense: last 6 weeks 75 % HR | 20 weeks | Candidate Gene |
| **Ring-Dimiriou et al. 2014** [40] | **N = 24** | Males only | 45–65 yrs | Austria | 4 | *PPARGC1A* | rs8192678 | GG (+) $VO_{2peak}$ | 70–90 % of Vo2peakk | 3 days/ week 10 weeks | Candidate Gene |
| **Rivera et al. 1997** [106] | N = 240 | Males (47.5 %) and Females | 17–65 yrs | HERITAGE study Caucasian and African-American U.S.A | 19 | *CKMM* | rs8111989 | CC (-) VO2max | Endurance training Moderate: at 55 % HR first two weeks and intense: last 6 weeks 75 % HR | 20 weeks | Candidate Gene |

▶ **Table 1** Continued.

| Author, Date | Sample Size | Sex (% Males) | Age | Ancestry/Country / ethnicity | Chromosome | Annotated gene | Variant | Genotype and training response (+/−/0) | Intervention (if any)/exercise | Dura-tion | Type of study |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Sonna et al. 2001** [107] | N = 147 | Males (42.2 %) and Female | Age 21.7 ± 3.6 yrs | USA: 57 % Cauca-sians, 25 % African-Ameri-cans, 14 % Hispanics, 3 % Asians, and 1 % Native American | 17 | *ACE* | rs1799752 | ACE I/D (0) $VO_{2max}$ | 2 aerobic days and 2 strength training days per week | 8 weeks | Candidate Gene |
| **Stefan et al. (2007)** [38] | N = 136 | Males (46 %) and Females | Age 19–67 yrs | Germany | 22<br>22<br>22<br>22<br>4 | *PPARD*<br>*PPARD*<br>*PPARD*<br>*PPARD*<br>*PPARGC1A* | rs2267668<br>rs6902123<br>rs2076167<br>rs1053049<br>rs8192678 | rs2267668 G (-) AT, $VO_{2peak}$<br>rs6902123 (0)<br>rs2076167 (0)<br>rs1053049 (0)<br>rs8192678 A (-) AT | Unsupervised: 3 h of moderate sports per week | 9 months | Candidate Gene |
| **Steinbacher et al. 2015** [41] | **N = 28** | Males Only | 50–69 yrs | Austria | 4 | *PPARGC1A* | rs8192678 | AA (-) decreased fibre type 1 transformation | 70–90 % of Vo2peakk | 3 days/ week 10 weeks | Candidate Gene |
| **Yoo et al. 2016** [108] | N = 79 | Males (64.6 %) and Females | Age 30–60 yrs | Korea | 12<br>18<br>2<br>3<br>6<br>2<br>2 | *AMN1*<br>*CDH2*<br>*ASB3*<br>*SRGAP3*<br>*UST*<br>*PUM2*<br>*KCNH7* | rs11051548<br>rs2542729<br>rs1451462<br>rs13060995<br>rs6570913<br>rs11096663<br>rs12613181 | (+) VO2 max<br>(+) VO2 max<br>(+) VO2 max<br>(+) VO2 max<br>(+) VO2 max<br>(+) VO2 max<br>(+) VO2 max | HIIT 60 %–84 % of VO2max | 9 weeks | GWAS |
| **Yu et al. 2014** [109] | N = 360 | Males (50 %) and Females | Age 18–40 yrs | China | 19 | *APOE* | E2, E3, E4 | E2/E3 (+) VO2max E3/E4 (+) VO2max | Aerobic 60 %–85 % | 6 months | Candidate gene |
| **Zarebska et al. 2014** [110] | N = 66 | Females only | Age 19–24 yrs | Caucasian Poland | 11 | *GSTP1* | rs1695 | G (+) VO2max and VEmax | Aerobic training 50 % to 70 % of HRmax | 12 weeks | Candidate gene |
| **Zhou et al. 2006** [111] | N = 102 | Males Only | 18.8 ± 0.9 yrs | China | 19 | *CKMM* | rs1803285 | AG (-) RE | Distance running program 95–105 % of VT | 18 weeks | Candidate Gene |

AT, Anaerobic Threshold; CO, Cardiac Output; VT, Ventilatory Threshold; RE, Running Economy; LVM, left ventricular mass; N/A, information not available; RP, Running Performance; SV, Stroke Volume.

▶ **Table 2** Gene variants associated with resistance trainability.

| Author, Date | Sample Size | Sex (% Males) | Age | Ancestry/ County of origin/ethnicity | Chromosome | Gene | Variant | Genotype and training response (+/−/0) | Intervention | Duration | Type of study |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Ash (2016)** [65] | N = 602 | Males (38.5 %) and Females | Age 18–40 yrs | FAMuSS study: Predominately European-American Ancestry | 5 | *NR3C1* | *rs10482614* *rs10482616* *rs4634384* | Females: rs4634384 T (+) Hypertrophy Males: rs10482616 GG (+) MVC rs10482614 AA (+) MVC | Upper arm, Unilateral resistance program | 12 weeks | Candidate Gene |
| **Charbonneau (2008)** [55] | N = 243 | Males (35.3 %) And Females | Age 50–85 yrs | U.SA. Caucasian | 17 | *ACE* | *rs1799752* | Females: ACE (0) Males: ACE (0) | Knee Extension unilateral resistance program | 10 weeks 3days/weeks | Candidate Gene |
| **Clarkson (2005)** [66] | N = 602 | Males (41 %) and Females | Age 18–40 yrs | FAMuSS study: Predominately European-American Ancestry | 11 | *ACTN3* | *rs1815739* | Females: ACTN3 XX (+) Maximal dynamic strength (1RM). Males: ACTN3 (0) | Upper arm, Unilateral resistance program | 12 weeks | Candidate Gene |
| **Delmonico (2007)** [112] | N = 157 | Males (45.2 %) and Females | Age = 50–85 yrs | Caucasian USA | 11 | *ACTN3* | *rs1815739* | Females: ACTN3 RR (+) PP Males: ACTN3 (0) | Knee Extension unilateral resistance program | 3days/week 10 weeks | Candidate Gene |
| **Erskine (2012)** [113] | N = 51 | Males only | Age 20.3 ± 3.1 yrs | Caucasian UK | 8 | *PTK2* | *rs7843014* *rs7460* | rs7843014 AA (+) Strength (MVC) *rs7460* TT (+) Strength (MVC) | Knee Extension unilateral resistance program | 3days/week 9 weeks | Candidate Gene |
| **Erskine (2013)** [61] | N = 51 | Males only | Age 20.3 ± 3.1 yrs | Caucasian UK | 17 11 | *ACE* *ACTN3* | *rs1799752* *rs1815739* | ACE (0) ACTN3 (0) | Knee Extension unilateral resistance program | 3days/week 9 weeks | Candidate Gene |
| **Folland (2000)** [56] | N = 33 | Males only | Age 18–30 yrs | UK | 17 | *ACE* | *rs4646994* | Isometric training: ACE DD/ID (+) Isometric strength (MVC) Dynamic training: ACE DD/ID (0) | Isometric Training Dynamic training | 3days/week 9 weeks | Candidate Gene |
| **Giaccaglia (2006)** [57] | N = 213 | Males (N/A) and Females | Age > 60 yrs | Predominately Males and Females of European-American Ancestry | 17 | *ACE* | *rs4646994* | ACE DD (+) strength (MVC) | Light resistance training | 3days/week 18 months | Candidate Gene |

▶ **Table 2** Continued.

| Author, Date | Sample Size | Sex (% Males) | Age | Ancestry/ County of origin/ethnicity | Chromosome | Gene | Variant | Genotype and training response (+/−/0) | Intervention | Duration | Type of study |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Harmon (2010)** [67] | N = 874 | Male (41.1%) and Females | Age 18–40 yrs | FAMuSS study: Predominately European-American Ancestry | 17<br>3 | *CCL2*<br>*CCR2* | *CCL2 (rs17652343), (rs1860189), (rs3917878), (rs2857654), (rs1024611), (rs1024610), (rs3760396), (rs2857656), (rs2857657), (rs4586), (rs13900)*<br>*CCR2 (rs17141010), (rs768539), (rs3918358), (rs1799864), (rs1799865).* | Females:<br>CCL2 (0) and CCR2 (0)<br>Males:<br>CCL2 T (rs1024610) (+)<br>Maximal Isometric strength (MVC)<br>Males and Females<br>CCR2 (AA) rs3918358 and (TT) rs1799865 (+)<br>Isometric strength (MVC) | Upper arm, Unilateral resistance program | 2 days/week<br>12 weeks | Candidate Gene |
| **He (2019)** [59] | N = 40 | Females only | Age 53–66 yrs | Chinese, Beijing | 17 | *ACE* | *rs4646994* | ACE DD (+) Maximal Isometric strength (MVC), muscle hypertrophy and grip strength | Whole body resistance training | 3 days/week<br>8 weeks | Candidate Gene |
| **Hong (2014)** [74] | N = 83 | Males only | Age<br>22.6 ± 1.4 yrs | South Korean | 11 | *CNTF* | *rs1800169* | CNTF G/A (0) | Resistance training of<br>the upper extremities | 3 days/week<br>8 weeks | Candidate Gene |
| **Jamshidi et al. (2002)** [114] | N = 144 | Males only | 19.6 (2.4) yrs | UK | 6 | *PPARA* | *rs425778* | C (+) LV mass | Upper and lower body training program | 10 weeks | Candidate Gene |
| **Jones (2006)** [13] | Study 1, N = 28.<br>Study 2<br>N = 39 | Males only | 18–20 yrs | Caucasian UK | 17<br>11 | *(Power-related polygenic risk score)* | *ACE D (rs1799752)*<br>*ACTN3 (rs1815739)*<br>*ADRB2 C (rs1042714)*<br>*AGT C (rs699)*<br>*IL-6 G/C (rs1800795)*<br>*PPARA C (rs4253778)*<br>*TRHR G (rs8192676)*<br>*VDR A (rs1544410)* | Power genotype (+)<br>Power (CMJ) after high intensity resistance training but not low intensity resistance training. | Low intensity (~30% of 1 RM and high repetitions) and high-intensity (~70% of 1 RM and low repetitions) resistance training | 8 weeks of high or low resistance training<br>1 to 2 days per week | Polygenic Score |

▶ **Table 2** Continued.

| Author, Date | Sample Size | Sex (% Males) | Age | Ancestry/ County of origin/ethnicity | Chromosome | Gene | Variant | Genotype and training response (+/−/0) | Intervention | Duration | Type of study |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Keogh (2015)** [115] | N = 58 | Males (31 %) and Females | Age 69.8 ± 5.3 | New Zealand (European ancestry) | 17 | *ACE*<br>*UCP2* | *rs4646994*<br>*rs7109266* | ACE ID (0)<br>UCP2 GG (+) Lower body strength (8ft Up and Go time) | Resistance training light to moderate intensity | 2days/week, 12 weeks | Candidate Gene |
| **Kostek (2005)** [116] | N = 67 | Males (47.7 %) and females | 50–85 yrs | U.S.A Caucasian | 12 | *IGF1* | *IGF1 192* | IGF1 192/192 + 192/- (+) dynamic (1RM) muscle strength | Unilateral resistance program | 10 weeks 3days/wk | Candidate Gene |
| **Li (2014)** [117] | N = 94 | Males only | Age 18–22 years | Han Chinese | 2 | *MTSN* | *rs1805086*<br>*rs1805065* | MTSN KR (+) Hypertrophy in Biceps and Quadriceps<br>MTSN AT + TT (+) Hypertrophy in Biceps | Arm and Leg resistance training | 3–4 days/ wk 8 weeks | Candidate Gene |
| **Pereira (2013)** [58] | N = 139 | Females only | Age 65.5 (8.2) | Portugal, Caucasian | 17<br>11 | *ACE*<br>*ACTN3* | *rs1799752*<br>*rs1815739* | ACE D/D (+) maximal dynamic strength 1RM, power (CMJ), functional capacity (STS)<br>ACTN3 RR (+) maximal dynamic strength (1RM), power (CMJ), functional capacity (STS) | High-speed power training | 12 weeks 3 days/week | Candidate Gene |
| **Pescatello (2006)** [60] | N = 631 | Males (42 %) and females | Age 18–40 yrs | FAMuSS study: Predominately European-American Ancestry | 17 | *ACE* | *rs4646994* | Trained Arm<br>Post Intervention: ACE II/ ID (+) Maximal Isometric strength (MVC)<br>Untrained Arm<br>Post Intervention: ACE DD/ID (+) maximal dynamic strength (1RM), muscle size (CSA of Type II fibres). | Upper arm, Unilateral resistance program | 12 weeks, 2 days/week | Candidate Gene |
| **Pistilli (2008)** [70] | N = 748 | Males (40.2 %) and Females | 18–40 yrs | Caucasian | 10 | *IL15RA* | *rs2296135* | *rs2296135* CC (+) MVC | RT program | 12 weeks 2 days/week | Candidate gene |
| **Reichman (2004)** [71] | N = 153 | Males (49.6 %) and Females | Aged 18–31 years | Predominantly European-American Ancestry | 10 | *IL15RA* | *rs3136617*<br>*rs3136618*<br>*rs2296135* | rs3136617 C (+) muscle hypertrophy<br>rs2296135 C (+) muscle hypertrophy | Whole body resistance training @75 % of 1RM | 10 weeks, 3 days/week | Candidate Gene |
| **Sprouse (2014)** [68] | N = 874 | Males (50 %) and females | Age: 18–40 years | FAMuSS study: Predominately European-American Ancestry | 8 | *SLC30A8* | *rs13266634* | Females: SCL30A8 (0)<br>Males: SCL30A8(0) | Upper arm, Unilateral resistance program | Acute and 12-week Intervention | Candidate Gene |

▶ **Table 2** Continued.

| Author, Date | Sample Size | Sex (% Males) | Age | Ancestry/ County of origin/ethnicity | Chromosome | Gene | Variant | Genotype and training response (+/−/0) | Intervention | Duration | Type of study |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Thomis (2004)** [63] | N = 57 | Males only | 22.4 (3.7) yrs | Flemish Brabant, Belgium | 17<br>2 | *ACE*<br>*MTSN* | *rs4646994*<br>*rs1805086*<br>*rs1805065* | ACE (I/D) (0) strength, isometric and concentric torque<br>or arm muscle cross-sectional area<br>MTSN: Unable to be determined | High resistance training program | 10 weeks, 3days/week | Candidate Gene |
| **Walsh (2009)** [73] | N = 745 | Males (40 %) and Females | Age 18–40 yrs | FAMuSS study: Predominately European-American Ancestry | 11 | *CNTF* | *rs1800169* | Females: CNTF GG (+) isometric (MVC) and dynamic (1RM) muscle strength<br>Males: CNTF (0) | Upper arm, Unilateral resistance program | 12 weeks, 2 days/wk | Candidate Gene |
| **Walsh (2012)** [69] | N = 560 | Males (N/A) and Females | Age 18–40 yrs | FAMuSS study: Predominately European-American Ancestry | 1 | *LEP*<br>*LEPR* | *rs2167270*<br>*rs1137100*<br>*rs1137101*<br>*rs1805096*<br>*rs8179183* | LEP (GG/GA) rs2167270 (+) Muscle hypertrophy<br>LEPR (0) | Upper arm, Unilateral resistance program | 12 weeks, 2 days/wk | Candidate Gene |

1RM, one maximal repetition; CMJ, counter movement jump; CSA, cross sectional area; LVM, Left ventricle mass; MVC, maximal voluntary contraction; N/A, information not available; RT, resistance training; STS, sit to stand test.

*PPARGC1A* locus itself, rather than individual SNPs located within that locus, may be important for trainability [43, 46].

Currently 26 SNPs associated with $VO_{2max}$ trainability were identified in a GWAS and were validated in 2 separate cohorts (detailed in ▶ **Table 2**) [23]. They accounted for 49 % of $VO_{2max}$ trainability and were able to classify responders and non-responders [23, 47]. Whether these SNPs are directly involved in gene function or regulation of genes is the next step to validate these findings. The most robust is the SNP rs6552828 located near the *ACSL1* gene which was the strongest predictor (~6 %) of aerobic trainability ($VO_{2max}$) [23]. It has subsequently been validated in a bioinformatics pathway analysis and found to be strongly correlated to the aerobic electron transport chain phenotype and the PPAR signalling pathway providing a robust candidate gene in $VO_{2max}$ trainability [31]. ACSL1 regulates lipid metabolism by facilitating the transport of long chain fatty acids into the mitochondria and is an essential step in fatty acid oxidation [48]. Timmons et al. integrated RNA profiles with genetic variants and found the following genes *CD44,* and *DAAM1,* also discovered in the Bouchard et al. GWAS, were associated with gene expression changes [49]. Gene expression of *CD44* was up-regulated in response to endurance training [49] and was strongly associated with phenotypic terms associated with aerobic exercise such as: cardiovascular physiological processes, muscle contraction, physical fitness and aerobic electron transport chain [31] indicating that this gene and any alterations to its function (i. e. via SNPs) may play in important role in aerobic trainability. While these genes certainly provide robust genes, there are still limitations in determining the causality of these particular SNPs in the molecular mechanisms affecting aerobic trainability.

Many candidate gene and GWAS studies have been conducted and this review highlights the large collection of candidate genes that have been associated with aerobic trainability. Only 12 SNPs have been robustly associated with aerobic trainability (▶ **Table 3**) meaning that have been validated in at least 2 independent cohorts and were shown to have some functional relevance. Subsequent studies should focus on understanding the functional role of the SNPs that have been replicated as this review highlights the lack of understanding of the molecular mechanism and limits our understanding of aerobic trainability.

## Resistance Trainability

Muscular strength and power show a heritability estimated around 52 % [14]. Skeletal muscle strength is defined as the force produced by muscle contraction. A variety of measures have been investigated, including muscle strength, maximal voluntary contraction (MVC), 1 repetition maximum (1RM) and handgrip strength. While the production of skeletal muscle power is defined as how much force can be produced and the velocity at which it is produced. The production of power can be measured at the by undertaking tests such as Wingate's, counter movement jumps (CMJ) and vertical jumps (VJ).

The *ACE I/D and ACTN3 R/X* SNPs are two of the most extensively studied gene loci. We have chosen not to discuss *ACTN3* here as it has recently been reviewed in detail by Del Coso et al. [50] and instead focus on the *ACE* I/D SNP. The *ACE* gene encodes the angiotensin-converting enzyme that is a central component of the renin-angiotensin-system [51]. The *ACE I/D* results in either an insertion (I) or deletion (D) of a 287-basepair region in intron 16 of the gene [52] and can alter the levels of ACE in the blood [52]. It has recently been shown that the polymorphism can manipulate the activity of the C- and N-terminal domain in the enzyme [53]. Further, exercise can decrease the enzyme activity in the C-terminal domain and increase the activity in the N- terminal domain which results in improved blood flow and proliferation of red blood cells [53]. It is thought that the I allele confers enhanced endurance performance while the D allele is thought to confer increased muscle power and strength [54]. The D allele was consistently shown across 6 separate candidate gene studies to be associated with greater gains in strength after resistance training and this was consistent across sex and age [55–60]. While the literature is consistent regarding muscular strength, the association with muscular power is less convincing [55, 61–63]. The D allele in *ACE* was associated with CMJ in older females after a 12-week power training program [58] and in young males after a high intensity training program [13]. However, it was the I allele in *ACE* that was associated with a higher

▶ **Table 3** Robust SNPs associated with aerobic or resistance trainability.

| **Aerobic trainability** | | | **Resistance trainability** | | |
|---|---|---|---|---|---|
| **SNP** | **Nearest gene** | **Beneficial allele** | **SNP** | **Nearest gene** | **Beneficial allele** |
| rs6552828 | *ACSL1* | G | rs4646994 * | *ACE* | D |
| rs699 | *AGT* | T | rs1799752 * | *ACE* | D |
| rs6090314 | *BIRC* | A | rs4340 * | *ACE* | D |
| rs12580476 | *C12orf36* | TBC | rs13447447 * | *ACE* | D |
| rs884736 | *CAMTA1* | G | rs1815739 | *ACTN3* | R |
| rs353625 | *CD44* | TBC | rs2296135 | *IL15 RA* | C |
| rs1956197 | *DAAM1* | G | rs4253778 | *PPARA* | C |
| rs17117533 | *NDN* | A | | | |
| rs8192678 | *PPARGC1A* | G | | | |
| rs10921078 | *RGS18* | A | | | |
| rs7531957 | *RYR2* | TBC | | | |
| rs11715829 | *ZIC4* | G | | | |

TBC, Allele to be confirmed; *Linkage Disequilibrium above 80 % according to ensemble LD calculator.

baseline VJ at baseline in males and females [62]. Another two studies did not find any association between the *ACE* I/D and skeletal muscle power at baseline or in response to resistance training [61, 63]. *ACE* provides a robust candidate gene for explaining variation in muscular strength but not muscular power suggesting that this gene loci may only explain some of the inter-individual resistance variability dependent on type of resistance exercise.

Many of the candidate genes in resistance trainability came from a large multi-centre trial (FAMuSS) which aimed to identify nonsynonymous SNPs with functional effects on muscle power and strength [64]. These include: *Glucocorticoid receptor (NR3C1)*[65], *alpha-actinin 3 (ACTN3)*[66], *Chemokine (C-C motif) ligand 2 (CCL2)*[67], *Chemokine (C-C motif) ligand 2 Receptor (CCR2)*[67], *ACE*[60], *Solute carrier family 30 (zinc transporter), member eight gene (SLC30A8)*[68], *Leptin (LEP)* and *Leptin receptor (LEPR)*[69]. The FAMuSS study was conducted in young (18–40 years old) males (N = 247) and females (N = 355) of predominantly European-American ancestry. Participants underwent a 12-week unilateral resistance program consisting of upper arm exercises in the non-dominant arm [60]. Only *IL-15RA, ACTN3* and *ACE* from this series of studies were replicated in separate cohorts and have functional relevance. In the *IL-15RA* locus the rs2296135 SNP was associated gains in muscular strength and replicated in two different studies in cohort of European ancestry [70, 71]. When the gene *IL-15RA* is knocked down in an animal model it altered the contractile properties and fatigability in skeletal muscle fibres [72]. While the locus is important it not yet clear which SNPs is responsible for altering the function of *IL-15RA* protein. Although SNPs within *CCL2, CCR2* and *CNTF* have not been replicated they interestingly showed sex-specific associations with muscle strength. *CTNF* polymorphisms were associated with strength gains only in females [73], which was subsequently confirmed in a South Korean cohort [74]. SNPs in *CCL2* and *CCR2* were associated strength gains in males only [67]. This indicates potential sex-specific differences in the genetic architecture of complex traits and should be incorporated into study design [75, 76]. In addition PTK2, CNTF, IL-6, PPARA and VDR candidate genes have been replicated with functional relevance [13, 73].

In total 7 SNPs (▶ **Table 3)** were robustly associated with resistance variability. While there are plethora of candidate gene studies no GWAS have been conducted that specifically focuses on resistance trainability.

## Functional Validation

We have identified 12 SNPs and 7 SNPs that are robustly associated with variance in aerobic and resistance trainability respectively. The next steps are to a) identify the causal SNP, b) annotate the casual SNP to the correct gene and then c) to establish the functional relevance of the gene [47]. The overall evidence from literature connecting causal genes to trainability is relatively low [31]. If we hope to identify the casual variants or genes it is vital that we begin to integrate "omic" technologies from the genome and epigenome to transcriptome to proteome and metabolome which can capture a complete picture of complex human traits such as aerobic and resistance trainability [77, 78].

There have been attempts to associate molecular pathways or "molecular phenotypes" with physiological phenotypes of aerobic and resistance trainability [79–81]. Sarzynski et al. applied this systems biology approach by combining the 21 SNP identified in a GWAS from the HERITAGE study cohort (▶ **Table 2**) [15, 23] and examined the joint contributions of these SNPs to exercise response [47]. This approach identified potential pathways in calcium signalling, energy sensing and partitioning, mitochondrial biogenesis, angiogenesis, immune functions, and regulation of autophagy and apoptosis, providing important pathways that can be investigated more closely [47]. Another integrative approach is expression quantitative trait loci (eQTLs) analysis that leverages gene loci identified from GWAS and integrate these with gene expression data to identify differential gene expression levels to try and uncover the 'molecular phenotype' that lead to these variations in exercise response [82, 83]. Willems et al. identified the rs6565586 SNP in *ACTG1* as a strong candidate gene in inter-individual variability in the resistance-related phenotype (hand grip strength) and correlated this with a lower expression of mRNA in skeletal muscle. *ACTG1* encodes Actin Gamma 1 and is involved in the structure and function of skeletal muscle fibres. Interestingly, in a knock out mouse model, animals displayed overt muscle weakness [84]. This type of analysis presented an ideal candidate gene to begin understanding the molecular mechanisms in human skeletal muscle.

To establish causality of genetic variants in aerobic and resistance trainability the field needs to move forward beyond association analysis. The type of follow-up experiment will depend on the location of SNP within the gene. For SNPs within coding regions ideally experiments are performed to study the effect of the SNP has on protein structure and function. For SNPs within in non-coding regions it more difficult to determine as they may not directly affect a gene but alter/regulate transcription factors and mediate alterations in genes this way [77]. However, with the introduction of the large epigenetic database ENCODE (Encyclopaedia of DNA elements) we can now identify the transcription factor association, chromatin structure and histone modification of target genes [85] and more recently enhancers providing candidate gene targets for follow up analysis [86]. With the discovery of CRISPR Cas-9 genome-editing tool in 2012 [87], this has paved the way for establishing causality of SNPs and the functional effects of them. This has been used to great effect for establishing causal genes implicated in insulin resistance whereby they were able to determine the casual effect of 12 candidate genes that had previously been identified in a GWAS [88]. To date no experiments have been conducted using this gene-editing tool to establish the function and causality of candidate genes of trainability beyond association analysis.

There is still much work to do before personalised exercise prescription (both in a clinical and elite athlete setting) can be based on an individual's genetics. However, there are concerted efforts taking place to make this possible such as the Athlome Project Consortium and the Gene SMART (Skeletal Muscle Response to Training), recently launched with the aim of uncovering the genetic variation underlying athletic performance, adaptation to exercise training, and exercise-related musculoskeletal injuries [89, 90]. These, and other initiatives will allow for population-based approach to understand the role of genes and environmental factors contributing to the complex exercise response phenotype [91].

This review summarised robust genetic variants that have been associated with aerobic and resistance trainability. To date, there is very little literature ascribed to understanding the interplay between genes and environmental factors and the development of physiological traits. Therefore, much work remains to identify causal variants and functional relevance of genes associated with aerobic and resistance trainability.

## Conflict of interest

The authors declare that they have no conflict of interest.

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