Mapping Robust Genetic Variants Associated with Exercise Responses

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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_2max) [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_2max 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 1	*ACE* *ATG*	rs4340 rs699	ACE (0) VO_{2max} TT (+) LVM	Moderate intensity endurance training	3 days/ week 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 6 9 3 9 3 1 1 20 11 14 15 11 14 2 4 11 3 22 11 6	*ACSL1* *PRDM1* *GRIN3A* *KCNH8* *C9orf27* *ZIC4* *CAMTA1* *RGS18* *BIRC7* *DBX1* *DAAM1* *NDN* *CXCR5* *TTC6* *LOC400950* *LOC100289626* *LOC100130460* *NLGN1* *MN1* *CD44* *ENPP3*	rs6552828 rs10499043 rs1535628 rs4973706 rs12115454 rs11715829 rs884736 rs10921078 rs6090314 rs10500872 rs1956197 rs824205 rs7933007 rs12896790 rs4952535 rs2053896 rs2198009 rs2030398 rs738353 rs353625 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* *MTND5*		MTN2 (-) VO_{2max} MTND5 (+) VO_{2max}	Endurance training at 85% of HRR	3–5 days/ week 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 rs2076167	African American only rs2016520 CC (-) $VO_{2max,}$ PPO 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 15	*NRF-1* *NRF-1* *NRF-2*	rs2402970 rs6949152 rs6949152	rs2402970 CC (+) VT, RE rs6949152 AA (+) VT, RE 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 15 15	*NRF-2* *NRF-2* *NRF-2*	rs12594956 rs8031031 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 4 4	*PPARGC1A* *PPARGC1A* *PPARGC1A*	rs17847357 rs8192678 rs6821591	rs17847357, rs8192678 (0) VO2max rs6821591 G (+) 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 4 4 2 9	*PPP3CA* *PPP3CA* *PPP3CA* *PPP3R1* *PPP3R2*	rs2850965 rs3804423 rs3804358 rs4671887 rs3739723	G (+) VO2max G (+) VO2max G (+) VO2max A (+) VO2max 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 8 8 8 8	*PPP3CC* *PPP3CC* *PPP3CC* *PPP3CC* *PPP3CC*	rs1879793 rs1075534 rs7430 rs2461483 rs10108011	CC (+) SV AA (+) SV, CO GG (+) SV CC (+) SV 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: GG (+) VO2max Females: (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 6 5 5 1	*PPARGC1A* *VEGF* *ADBR2* *ADBR2* *CRP*	rs8192678 rs2010963 rs1042713 rs1042714 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 22 22 22 4	*PPARD* *PPARD* *PPARD* *PPARD* *PPARGC1A*	rs2267668 rs6902123 rs2076167 rs1053049 rs8192678	rs2267668 G (-) AT, VO_{2peak} rs6902123 (0) rs2076167 (0) rs1053049 (0) 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 18 2 3 6 2 2	*AMN1* *CDH2* *ASB3* *SRGAP3* *UST* *PUM2* *KCNH7*	rs11051548 rs2542729 rs1451462 rs13060995 rs6570913 rs11096663 rs12613181	(+) VO2 max (+) VO2 max (+) VO2 max (+) VO2 max (+) VO2 max (+) VO2 max (+) 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 3	*CCL2* *CCR2*	*CCL2 (rs17652343), (rs1860189), (rs3917878), (rs2857654), (rs1024611), (rs1024610), (rs3760396), (rs2857656), (rs2857657), (rs4586), (rs13900)* *CCR2 (rs17141010), (rs768539), (rs3918358), (rs1799864), (rs1799865).*	Females: CCL2 (0) and CCR2 (0) Males: CCL2 T (rs1024610) (+) Maximal Isometric strength (MVC) Males and Females CCR2 (AA) rs3918358 and (TT) rs1799865 (+) Isometric strength (MVC)	Upper arm, Unilateral resistance program	2 days/week 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 8 weeks	Candidate Gene
Hong (2014) [74]	N = 83	Males only	Age 22.6 ± 1.4 yrs	South Korean	11	*CNTF*	*rs1800169*	CNTF G/A (0)	Resistance training of the upper extremities	3 days/week 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. Study 2 N = 39	Males only	18–20 yrs	Caucasian UK	17 11	*(Power-related polygenic risk score)*	*ACE D (rs1799752)* *ACTN3 (rs1815739)* *ADRB2 C (rs1042714)* *AGT C (rs699)* *IL-6 G/C (rs1800795)* *PPARA C (rs4253778)* *TRHR G (rs8192676)* *VDR A (rs1544410)*	Power genotype (+) 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 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* *UCP2*	*rs4646994* *rs7109266*	ACE ID (0) 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* *rs1805065*	MTSN KR (+) Hypertrophy in Biceps and Quadriceps 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 11	*ACE* *ACTN3*	*rs1799752* *rs1815739*	ACE D/D (+) maximal dynamic strength 1RM, power (CMJ), functional capacity (STS) 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 Post Intervention: ACE II/ ID (+) Maximal Isometric strength (MVC) Untrained Arm 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* *rs3136618* *rs2296135*	rs3136617 C (+) muscle hypertrophy 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) 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 2	*ACE* *MTSN*	*rs4646994* *rs1805086* *rs1805065*	ACE (I/D) (0) strength, isometric and concentric torque or arm muscle cross-sectional area 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 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* *LEPR*	*rs2167270* *rs1137100* *rs1137101* *rs1805096* *rs8179183*	LEP (GG/GA) rs2167270 (+) Muscle hypertrophy 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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