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GENETIC AND MORPHOLOGICAL DETERMINANTS OF ATHLETIC PERFORMANCE: INSIGHTS INTO EXERCISE ADAPTATION, MUSCULAR FUNCTION, AND PHYSICAL FITNESS

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ABSTRACT:
The actions of skeletal-muscle molecular regulation, morphology, and the function of skeletal muscle, and training-specific physiological adaptation, all interact to affect athletic performance. Combining these domains may provide some explanation for the differences in performance between resistance and endurance training and concurrent exercise training. This study compared physiological and skeletal-muscle transcriptomic adaptations across training modes and explored associations between exercise-responsive genes and individual changes in physical performance. Paired pre- and post-training data were analyzed from 18 healthy young men who completed 12 weeks of resistance, endurance, or concurrent training. Nine morphological and performance outcomes were assessed using nonparametric tests with multiplicity correction. RNA-sequencing counts from 36 skeletal-muscle samples were analyzed using paired DESeq2 models, followed by functional enrichment and gene–phenotype correlation analyses. Maximal aerobic power increased after concurrent and endurance training but decreased after resistance training, representing the only physiological outcome with a significant Holm-adjusted between-group difference (adjusted $p = 0.030$). Concurrent training produced 351 differentially expressed genes, compared with 50 after endurance training and 16 after resistance training. Concurrent and endurance responses were dominated by collagen and extracellular-matrix remodeling, whereas resistance training enriched muscle-contraction, myofibril-assembly, complement, and fatty-acid metabolic processes. Five of 234 gene–phenotype correlations were nominally significant, but none survived false-discovery-rate correction. Training mode played a key role in exercise adaptation, with functional and transcriptional differences. A comprehensive, integrated molecular and physiological evaluation can help explain the process of athletic adaptation, but cannot determine the effects of a single gene.

KEYWORDS: exercise adaptation, skeletal muscle transcriptomics, athletic performance, muscular function, physical fitness

1. INTRODUCTION

The interplay of genetics, skeletal-muscle properties, body fat composition, training history, nutrition and recovery are all determinants in athletic performance. Strength, power and endurance are not individual characteristics, but the result of the interaction between neuromuscular, metabolic, cardiovascular and morphological systems. Several variants have been identified from genetic studies that play a role in muscle function, oxygen transport, energy metabolism and responsiveness to training, but the effect of these variants is small and context-dependent (Semenova et al., 2023). These relationships are also affected by nutritional status, as micronutrient deficiencies (iron, vitamin D, and micronutrients) may hinder oxygen supply, energy production, recovery, and training stability (Beck et al., 2021). The molecular basis of performance is dynamic and not a set of genes. Transcription, translation, regulation of mitochondria, turnover of extracellular matrix, vascular signaling and substrate utilization are all affected by exercise in skeletal muscle. These responses relate to cellular mechanisms and measurable changes in strength, aerobic capacity, and power (Furrer et al., 2023). While variants in ACTN3, ACE, and energy regulation genes are important, there is no single set of polymorphisms that can account for athletic ability (Cerit et al., 2020). There may also be physiological differences at the population level which are not just racial; they could be a combination of ancestry,

environment, opportunity and training history, thus rendering racial categories inappropriate for direct biological measurement (Hunter, 2017).

Muscular strength is part of athletic performance, helping to develop force, sprint, jump, economy of effort and protection from injury. It is dependent on the intensity, volume, specificity, and athletes' ability to achieve progressive overload (Suchomel et al., 2018). Skeletal muscle is a highly heterogeneous and adaptable tissue, with a variety of contractile proteins, connective tissue, vascular system, metabolic machinery, and cell types (Mukund & Subramaniam, 2020). These changes in the tissue due to training may include alterations in extracellular matrix organization, myofibrillar remodeling, inflammatory regulation, angiogenesis and changes in metabolic gene expression. Another method of determining performance is by morphological characteristics. Lean mass, fat mass, body size and distribution of tissues affect the production of force, efficiency of movement, thermoregulation, and cost of exercise. Body-composition assessment has progressed from total mass to evaluating the distribution of tissues in the body and compartments relevant to function (Lukaski & Raymond-Pope, 2021). Muscle amount is not sufficient to depict performance potential, as the quality of skeletal muscle (metabolic condition, muscle architecture, and strength per muscle mass) is more important (Naimo et al., 2021). Combining morphological, molecular, and functional measurements may thus be a more useful story than any single component alone.

The added complexity of training mode is due to the different, but related, biological demands of resistance and endurance training. Endurance training is important for increasing oxidative capacity, cardiovascular function, and fatigue resistance, while resistance training is important for neural adaptations, maximal force, power, and muscle remodeling. Concurrent training is a training approach that is designed to train both capacities in the same program, but this dual stimulus can alter adaptations due to the differences in stimulus, recovery, or molecular signaling. There are indications that resistance, endurance, and concurrent programs can have different patterns of performance and anthropometric alterations when applied to active populations (Prieto-González & Sedlacek, 2022). There is still significant variation in individual response for each training mode. The effects of the variation are context-dependent and may impact vascular regulation, muscle phenotype and exercise adaptation, but not necessarily any one of these pathways alone (Sjúrðarson & Nordsborg, 2025). Transcriptional and metabolic remodeling has been recorded in human exercise studies, but the data were collected and analyzed at varying time points, in different tissues, and by researchers of different ages, and the techniques used for data analysis differ. However, comparisons between studies are difficult due to differences in the time point at which samples were taken, in tissue type, in participant characteristics, and in the methods used to analyze the data, in human exercise studies (Lavin et al., 2022). New methods are becoming increasingly adopted that integrate genomics, transcriptomics, physiological monitoring and digital phenotyping to describe performance as a multi-dimensional, time-dependent trait (Juginović et al., 2025).

There is a gap in research in combining the responses of the transcriptome with morphological, aerobic, and anaerobic adaptations of skeletal muscle in response to various training modalities. Numerous studies examine a single genetic variant, exercise outcome or a single type of exercise. Relatively few studies compare muscle responses of pairs of muscle samples taken from the same individual to determine if they are common or specific to resistance or endurance training or concurrent training. However, there is also a lack of evidence on whether gene changes related to exercise responsiveness are associated with changes in exercise capacity (strength, body composition, oxygen uptake, anaerobic power) after controlling for training group differences and multiple testing.

To fill this void, the present study compared molecular and physical factors involved in exercise adaptation in healthy young men who were concurrently trained, resistance trained, and endurance trained. It sought to quantify changes in morphology, muscular function, aerobic capacity and anaerobic performance; to look for common and training-specific genes that changed their expression and enriched biological functions; and to assess the relationship between the most prominent changes in gene expression and individual physiological changes. The integrated framework was developed to help explain the changes in the responses of skeletal muscle to training and the connection between these responses and the measurable aspects of athletic performance.

2. METHODOLOGY

2.1 Research Design

A secondary longitudinal analysis was performed to address the molecular, morphological, muscular and physical-fitness responses to exercise training. Six young healthy men in each of the three groups took part in a 12-week regimen of either concurrent resistance and endurance training (CET), endurance training (END), or resistance training (RES). Physiological measurements and skeletal-muscle samples were taken before and after training and compared between the three interventions.

2.2 Data Source

The data were publicly downloaded from the Gene Expression Omnibus (GSE137832), which was previously published by Shamim (2020). The 18 healthy young men were randomized to either CET, END, or RES and gene-expression profiling was carried out in samples of skeletal muscle on the Ion Torrent S5 XL platform. Data

analysed comprised 36 matched samples (one pre and one post-training sample for each participant) and gene annotations, as well as paired physiological measures.

2.3 Morphological and Physical-Performance Analysis

The physiological file was matched with the transcriptomic file, and one non-participant note row was dropped. The outcomes evaluated were: Body Mass, BMI, Lean Body Mass, Fat Mass, 1RM on leg press, Knee extension performance, Peak Oxygen Uptake, Maximal Aerobic Power and Wingate peak power. Absolute adaptation was found by subtracting the pre-training value from the post-training value.

Data regarding the basic parameters were given as mean and standard deviation values and compared by Kruskal–Wallis tests. Changes within groups were analyzed with paired Wilcoxon signed-rank tests, and the magnitude of the changes was quantified by rank-biserial correlations. The differences in change among the three groups (CET, END, RES) were compared respectively via Kruskal–Wallis tests and epsilon-squared effect sizes. Pairwise comparisons that were relevant were performed using Dunn's tests, and Holm correction was applied for multiple testing.

2.4 Transcriptomic Analysis

The original count matrix was comprised of 39,376 genes from 36 pairs of skeletal muscles. We were able to annotate human genes to the genes and retain those with a minimum of 10 counts in at least six samples, leaving 13,967 genes to analyze. Library size, number of genes detected, variance-stabilized sample correlation, PCA of the 500 most variable genes, and Cook's-distance diagnostics were used to assess the quality.

Paired negative binomial models in DESeq2 were used for each of the three categories of expression (CET, END, and RES). To accommodate the repeated pre–post design, participant identity and sampling time were included in each model. Log_2 fold changes were stabilized using apeglm shrinkage. Genes were labeled as being differentially expressed if both the adjusted p-value was < 0.05 and the absolute value of the shrunken log_2 fold change was ≥ 0.50.

2.5 Functional and Integrated Analysis

The molecular responses were compared between the three training groups to find common (and training-specific) responses. To identify the biological processes, molecular functions and cellular components, Gene Ontology enrichment analysis was carried out with a reference background of 13,967 genes tested. Enrichment p-values were adjusted using the Benjamini-Hochberg procedure, and $p<0.05$ was considered significant.

Changes in the expression of 26 key genes that respond to exercise were assessed and correlated with changes in the nine morphological and performance measures examined to identify molecular mechanisms that mediate physiological adaptation. Changes in gene expression and physiology were calculated for each training group separately by subtracting their minimum from their maximum. Spearman correlations were performed for the 18 participants, and False Discovery Rate correction was performed across the 234 gene-phenotype comparisons. The adjusted p-value of < 0.05 was considered significant, whereas unadjusted associations were considered exploratory.

3. RESULTS

3.1 Baseline characteristics

The number of participants in the analysis was 18, equally distributed between the three groups (concurrent training, endurance training and resistance training), with 6 participants for each. Physiological measures were available for all participants before and after intervention. The overall mean age was 22.61 ± 4.10 years, and the mean height was 1.80 ± 0.07 m. Baseline body mass ranged from 74.30 ± 7.24 kg in END to 82.27 ± 10.11 kg in CET. There were no statistically significant differences in age, height, body mass, BMI, lean body mass, fat mass, muscular strength, aerobic fitness and anaerobic power among the training groups at baseline. There were no statistically significant differences between groups for BMI ($H = 4.351$, $p = 0.114$) or age ($H = 3.960$, $p = 0.138$); the largest baseline group differences were observed for these. The three groups were, therefore, similar before the intervention. Table 1 presents the demographic, morphological, muscular-function and physical-fitness baseline variables of the study participants.

Table 1. Baseline characteristics of participants according to training group

Characteristic	CET, mean ± SD	END, mean ± SD	RES, mean ± SD	Overall, mean ± SD	Kruskal–Wallis H	p-value
Age (years)	25.33 ± 3.88	21.50 ± 4.04	21.00 ± 3.52	22.61 ± 4.10	3.960	0.138
Height (m)	1.78 ± 0.07	1.79 ± 0.05	1.83 ± 0.10	1.80 ± 0.07	0.390	0.823
Body mass (kg)	82.27 ± 10.11	74.30 ± 7.24	75.78 ± 11.37	77.45 ± 9.81	2.000	0.368
Body mass index (kg/m²)	25.95 ± 3.19	23.08 ± 1.79	22.62 ± 2.27	23.88 ± 2.78	4.351	0.114
Lean body mass (kg)	60.40 ±	57.63 ±	60.03 ±	59.36 ± 6.54	0.421	0.810

	6.18	5.34	8.56			
Fat mass (kg)	19.07 ± 7.12	14.02 ± 3.85	12.57 ± 4.59	15.22 ± 5.80	3.079	0.214
Leg press one-repetition maximum (kg)	272.08 ± 72.91	239.17 ± 42.71	242.08 ± 79.28	251.11 ± 64.68	1.267	0.531
Knee-extension performance (kg)	122.50 ± 44.02	109.17 ± 14.55	111.67 ± 25.82	114.44 ± 29.39	0.247	0.884
Peak oxygen uptake (L/min)	3.36 ± 0.70	3.51 ± 0.37	3.55 ± 0.74	3.47 ± 0.60	0.713	0.700
Maximal aerobic power (W)	252.17 ± 59.98	266.67 ± 29.17	274.33 ± 70.99	264.39 ± 53.67	1.267	0.531
Wingate peak power (W)	884.00 ± 155.95	805.00 ± 169.24	867.50 ± 200.12	852.17 ± 169.06	0.561	0.755

Note: CET, concurrent resistance and endurance training; END, endurance training; RES, resistance training; SD, standard deviation. P-values were calculated using exploratory Kruskal–Wallis tests.

3.2 Physiological adaptations following training

Physiological adaptation was different in each of the training conditions with respect to both the direction and intensity. Leg press one-repetition maximum increased by 64.58 ± 25.32 kg in RES and 56.25 ± 45.65 kg in CET, compared with 11.67 ± 21.37 kg in END. The difference was not significant after Holm correction (adjusted $p = 0.216$), but it was significant between groups without adjustment ($p = 0.036$; $\varepsilon^2 = 0.310$). Knee-extension performance increased by 51.67 ± 20.66 kg in RES, 46.67 ± 23.17 kg in CET, and 19.17 ± 9.31 kg in END. The group difference was significant, unadjusted $p = 0.027$, and there was a moderate to large effect size, $\varepsilon^2 = 0.350$, but the group difference was not significant, adjusted $p = 0.186$. Peak oxygen uptake increased by 0.38 ± 0.17 L/min in CET and 0.43 ± 0.31 L/min in END, whereas RES demonstrated a mean decrease of 0.07 ± 0.27 L/min. This unadjusted comparison was significant ($p = 0.022$; $\varepsilon^2 = 0.377$), but failed to withstand multiplicity correction (adjusted $p = 0.174$).

Maximal aerobic power increased by 44.50 ± 10.09 W in CET and 46.33 ± 16.73 W in END but decreased by 12.33 ± 7.61 W in RES. The largest between-group effect ($\varepsilon^2 = 0.626$) and the only physiological measure that was still statistically significant after Holm correction ($H = 11.383$, unadjusted $p = 0.003$, adjusted $p = 0.030$) was this outcome. Wingate peak power increased most strongly in RES (123.33 ± 51.15 W), followed by END (64.83 ± 40.85 W). The CET answer was smaller and significantly more variable (29.50 ± 112.68 W). The overall unadjusted comparison was just outside the nominal significance boundary ($p = 0.050$; $\varepsilon^2 = 0.267$), but not significant once corrected (adjusted $p = 0.249$). Lean body mass increased by 2.63 ± 1.50 kg in CET, 2.22 ± 0.81 kg in END, and 2.27 ± 1.23 kg in RES, with no evidence of a between-group difference. The changes in body mass, BMI and fat mass were also not significantly different between the training groups. Table 2 presents the pre- and post-intervention, and absolute-change results for physiological outcomes.

Table 2. Physiological adaptations according to training group

Outcome	Group	Pre, mean ± SD	Post, mean ± SD	Change, mean ± SD	Paired p-value	Paired Holm p-value	Between-group p-value	Between-group Holm p-value	ε^2
Body mass (kg)	CET	82.27 ± 10.11	85.27 ± 8.04	3.00 ± 4.13	0.094	0.375	0.524	1.000	0.000
Body mass (kg)	END	74.30 ± 7.24	76.75 ± 7.77	2.45 ± 2.07	0.062	0.312	0.524	1.000	0.000
Body mass (kg)	RES	75.78 ± 11.37	79.35 ± 12.34	3.57 ± 2.07	0.031	0.281	0.524	1.000	0.000
Body mass index (kg/m²)	CET	25.95 ± 3.19	26.93 ± 2.43	0.98 ± 1.24	0.094	0.375	0.494	1.000	0.000
Body mass index (kg/m²)	END	23.08 ± 1.79	23.83 ± 1.60	0.75 ± 0.65	0.094	0.312	0.494	1.000	0.000
Body mass index (kg/m²)	RES	22.62 ± 2.27	23.68 ± 2.58	1.07 ± 0.56	0.031	0.281	0.494	1.000	0.000
Leg press one-repetition maximum (kg)	CET	272.08 ± 72.91	328.33 ± 72.57	56.25 ± 45.65	0.062	0.312	0.036	0.216	0.310

Leg press one-repetition maximum (kg)	END	239.17 ± 42.71	250.83 ± 44.21	11.67 ± 21.37	0.312	0.625	0.036	0.216	0.310
Leg press one-repetition maximum (kg)	RES	242.08 ± 79.28	306.67 ± 58.62	64.58 ± 25.32	0.031	0.281	0.036	0.216	0.310
Knee-extension performance (kg)	CET	122.50 ± 44.02	169.17 ± 34.99	46.67 ± 23.17	0.031	0.281	0.027	0.186	0.350
Knee-extension performance (kg)	END	109.17 ± 14.55	128.33 ± 18.07	19.17 ± 9.31	0.031	0.281	0.027	0.186	0.350
Knee-extension performance (kg)	RES	111.67 ± 25.82	163.33 ± 29.44	51.67 ± 20.66	0.031	0.281	0.027	0.186	0.350
Peak oxygen uptake (L/min)	CET	3.36 ± 0.70	3.74 ± 0.57	0.38 ± 0.17	0.031	0.281	0.022	0.174	0.377
Peak oxygen uptake (L/min)	END	3.51 ± 0.37	3.94 ± 0.49	0.43 ± 0.31	0.031	0.281	0.022	0.174	0.377
Peak oxygen uptake (L/min)	RES	3.55 ± 0.74	3.47 ± 0.61	−0.07 ± 0.27	0.312	0.312	0.022	0.174	0.377
Maximal aerobic power (W)	CET	252.17 ± 59.98	296.67 ± 52.69	44.50 ± 10.09	0.031	0.281	0.003	0.030	0.626
Maximal aerobic power (W)	END	266.67 ± 29.17	313.00 ± 39.92	46.33 ± 16.73	0.031	0.281	0.003	0.030	0.626
Maximal aerobic power (W)	RES	274.33 ± 70.99	262.00 ± 68.31	−12.33 ± 7.61	0.031	0.281	0.003	0.030	0.626
Wingate peak power (W)	CET	884.00 ± 155.95	913.50 ± 115.04	29.50 ± 112.68	1.000	1.000	0.050	0.249	0.267
Wingate peak power (W)	END	805.00 ± 169.24	869.83 ± 189.03	64.83 ± 40.85	0.062	0.312	0.050	0.249	0.267
Wingate peak power (W)	RES	867.50 ± 200.12	990.83 ± 189.04	123.33 ± 51.15	0.031	0.281	0.050	0.249	0.267
Lean body mass (kg)	CET	60.40 ± 6.18	63.03 ± 6.12	2.63 ± 1.50	0.031	0.281	0.728	1.000	0.000
Lean body mass (kg)	END	57.63 ± 5.34	59.85 ± 5.65	2.22 ± 0.81	0.031	0.281	0.728	1.000	0.000
Lean body mass (kg)	RES	60.03 ± 8.56	62.30 ± 8.35	2.27 ± 1.23	0.031	0.281	0.728	1.000	0.000
Fat mass (kg)	CET	19.07 ± 7.12	19.55 ± 4.61	0.48 ± 2.88	0.844	1.000	0.523	1.000	0.000
Fat mass (kg)	END	14.02 ± 3.85	14.38 ± 3.23	0.37 ± 1.72	0.312	0.625	0.523	1.000	0.000
Fat mass (kg)	RES	12.57 ± 4.59	14.20 ± 5.76	1.63 ± 1.91	0.094	0.281	0.523	1.000	0.000

Note: Within-group comparisons used Wilcoxon signed-rank tests. Between-group comparisons used Kruskal–Wallis tests of absolute change. Holm-adjusted p-values account for multiple testing. ε^2 represents epsilon-squared effect size.

The result with the most significant between-group difference was displayed for each physiological domain as shown in Figure 1. Figure 1A indicates that the maximal aerobic power increased for CET and decreased for RES. As seen in Figure 1B, the improvement in peak power in the RES sector was the greatest, the END sector was intermediate and the CET sector was highly variable. The majority of body-mass changes in Figure 1C are positive, but there is no apparent training-specific separation. In resistance training (RES) and concurrent resistance and endurance training (CET), knee-extension improvements are greater than in END (Figure 1D).

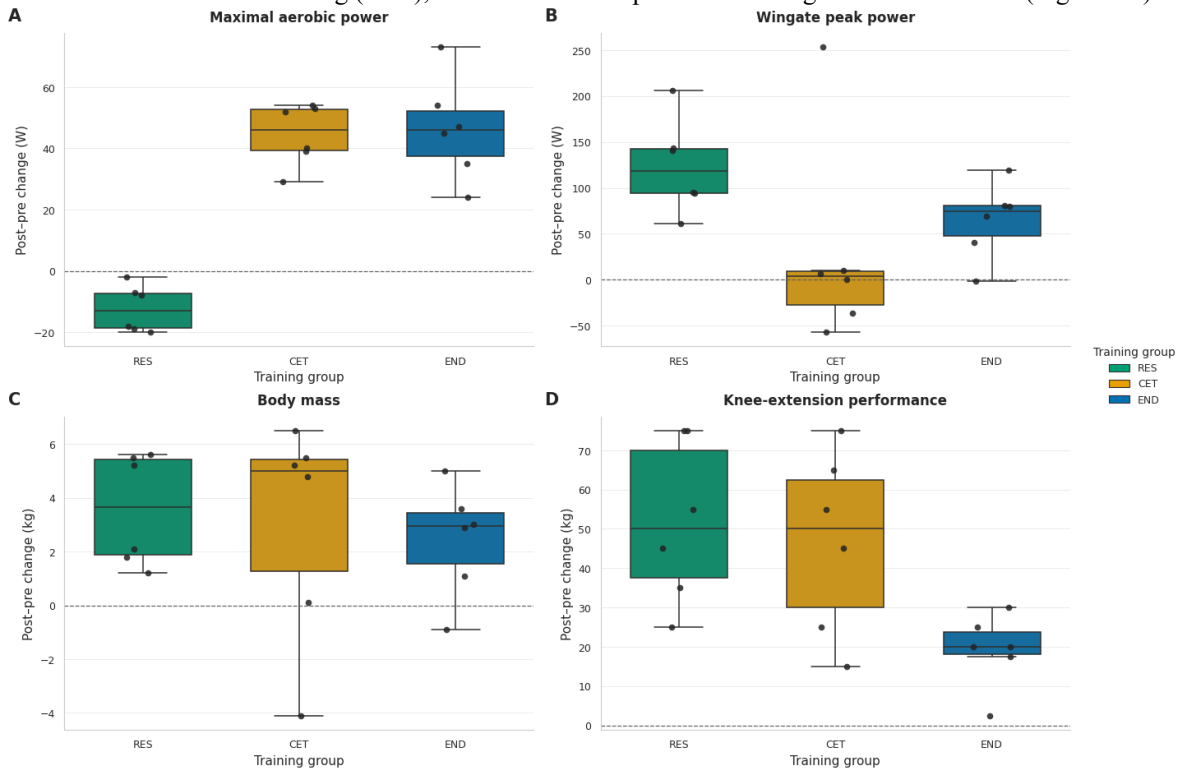

Figure 1. Physiological adaptations following exercise training: (A) maximal aerobic power; (B) Wingate peak power; (C) body mass; and (D) knee-extension performance.

3.3 Transcriptomic quality and global expression variation

The initial RNA-sequencing matrix was for 39,376 genes and 36 samples. Of this number, 16,507 genes showed no counts in any of the samples. The expression, filter, applied 13,967 genes with 10 or more counts in six or more samples. Library sizes ranged from 5,097,132 to 21,712,627 reads, while the number of detected genes per sample ranged from 15,655 to 18,076. The 34.56% and 10.30% of the transcriptomic variance was accounted for by PC1 and PC2, respectively, for a total of 44.86%. The majority of samples clustered together in the PCA plot and some END samples were scattered along PC1. Participant-specific transcriptomic responses were reflected in individual pre–post trajectories as the direction and magnitude of these trajectories varied. The median value of the correlation coefficient for all sample pairs was 0.968, and the range of correlation coefficients was from 0.764 to 0.989. Correlations between the pairs of pre–post were higher, from 0.900 to 0.989 (median 0.979). Participant P24 in END had the lowest paired correlation (r = 0.900), followed by P30 in END (r = 0.954) and P29 in CET (r = 0.963). Four samples have one gene that is above the model specific influence threshold when applying cook's distance diagnostics. Pre and post training measurements of P26 (CET) and P24 (END) are shown in these samples. The top score of a participant was 0.000072 (affected proportion of evaluated genes) and none had a broad transcriptomic effect. All samples were thus kept. The global structure of the transcriptomic network and the similarity of expression among transcripts within participants is depicted in Figure 2. The pre–post trajectories of individual participants are plotted in PCA space in Figure 2A, colored by the training group in which they participated and shaped by the time of training. A higher correlation between paired expressions was consistently found across the three training groups in Figure 2B than in Figure 2A, which had a comparatively lower correlation in END.

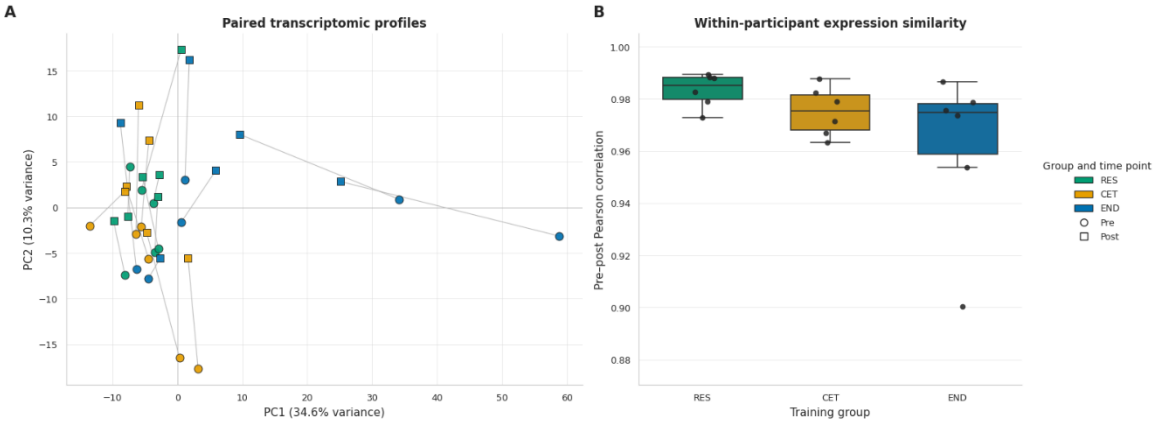

Figure 2. Transcriptomic variation and paired-sample quality: (A) principal component analysis of the 500 most variable genes with individual pre–post trajectories; and (B) within-participant pre–post expression correlations.

3.4 Differential gene expression following training

Each of the training groups was evaluated for 13,967 genes in a paired differential-expression model. The largest transcriptomic response that was observed was from CET with 351 significant genes, of which 291 were upregulated and 60 were downregulated. END yielded 50 significant genes (44 upregulated and 6 downregulated genes). Out of 16 significant genes produced by RES, 5 were upregulated, and 11 were downregulated. The most prominent response of the genes was the leading response of CET in THY1 (shrunken $\log_2$ fold change = 2.584; adjusted p = 3.961×10^{-15}). Other genes were found to have strong upregulation, such as SFRP2, COL4A1, and CPXM1, while CALML6 was strongly downregulated. Other key CET genes that were identified were those involved with the extracellular matrix (ECM), such as COL4A2, COL3A1 and ELN. In END, CAPN6 had the smallest adjusted p-value (shrunken $\log_2$ fold change = 2.545; adjusted p = 1.455×10^{-10}). Other top genes that were upregulated were CPXM1, COL4A2, COL4A1, COL1A2, SPARC, COL5A1, MXRA5 and LUM. The majority of the fold changes were positive, which showed that the END response was mostly based on transcriptional activation. The RES response was less pronounced and comprised more genes that were downregulated. The top upregulated gene was ASPN (adjusted p-value = 0.0015), and the top downregulated gene was PI16 (adjusted p-value = 0.0015). Other important genes that were associated with the RES were SPARC, MYH6, PTGDS, CFD, C3, CNTFR, OTUD1, and ELL2. The top 5 differentially expressed genes for each training set are displayed in Table 3.

Table 3. Leading differentially expressed genes following each training intervention

Training group	Rank	Gene ID	Gene symbol	Gene description	Base mean	Shrunken $\log_2$ fold change	Direction	p-value	Adjusted p-value
CET	1	7070	THY1	Thy-1cell surface antigen	188.92	2.584	Upregulated	2.892×10^{-19}	3.961×10^{-15}
CET	2	6423	SFRP2	Secreted frizzled-related protein 2	42.78	2.958	Upregulated	1.502×10^{-18}	1.028×10^{-14}
CET	3	1282	COL4A1	Collagen type IV alpha 1 chain	638.71	1.448	Upregulated	5.347×10^{-17}	2.441×10^{-13}
CET	4	56265	CPXM1	Carboxypeptidase X, M14 family member 1	53.68	3.369	Upregulated	5.783×10^{-16}	1.980×10^{-12}
CET	5	163688	CALML6	Calmodulin-like 6	506.39	−2.009	Downregulated	7.703×10^{-16}	2.110×10^{-12}
END	1	827	CAPN6	Calpain 6	114.53	2.545	Upregulated	1.041×10^{-14}	1.455×10^{-10}
END	2	56265	CPXM1	Carboxypeptidase X, M14 family member 1	54.17	3.351	Upregulated	2.624×10^{-12}	1.832×10^{-8}
END	3	1284	COL4A2	Collagen type IV	767.89	1.121	Upregulated	1.30	6.062

				alpha 2 chain				2×10^{-9}	$\times 10^{-6}$
END	4	1282	COL4A1	Collagen type IV alpha 1 chain	766.29	1.266	Upregulated	1.422×10^{-8}	4.172×10^{-5}
END	5	1278	COL1A2	Collagen type I alpha 2 chain	2502.46	1.614	Upregulated	1.494×10^{-8}	4.172×10^{-5}
RES	1	54829	ASPN	Asporin	135.58	1.086	Upregulated	1.662×10^{-7}	1.505×10^{-3}
RES	2	221476	PI16	Peptidase inhibitor 16	187.39	−0.896	Downregulated	2.386×10^{-7}	1.505×10^{-3}
RES	3	6678	SPARC	Secreted protein acidic and cysteine rich	5357.30	0.749	Upregulated	1.834×10^{-6}	7.709×10^{-3}
RES	4	1271	CNTFR	Ciliary neurotrophic factor receptor	178.04	−0.586	Downregulated	8.237×10^{-6}	1.922×10^{-2}
RES	5	4624	MYH6	Myosin heavy chain 6	596.99	0.566	Upregulated	1.028×10^{-5}	1.922×10^{-2}

Note: Genes were classified as differentially expressed when the adjusted p-value was below 0.05, and the absolute shrunken $\log_2$ fold change was at least 0.5. Positive fold changes indicate higher post-training expression.

The magnitude, direction, and statistical significance of the transcriptional responses are displayed in Figure 3. The red and blue arrows represent the direction of the genes in Figure 3A that were significantly up- or down-regulated by the restricted RES response. Figure 3B depicts the widespread CET response, including 351 significant genes with a clear predominance of upregulation. The intermediate END response is shown in Figure 3C (50 genes, most of which are upregulated).

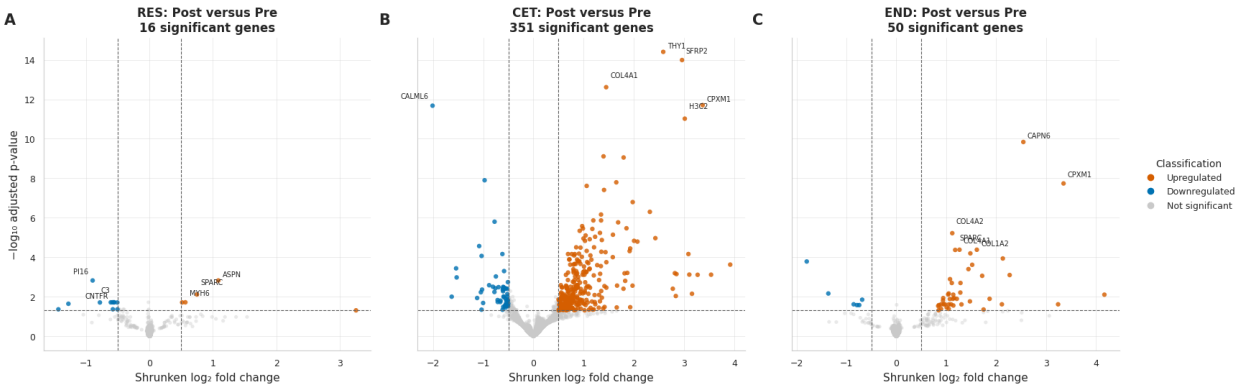

Figure 3. Training-specific skeletal-muscle differential expression: (A) resistance training post-intervention versus pre-intervention; (B) concurrent training post-intervention versus pre-intervention; and (C) endurance training post-intervention versus pre-intervention

3.5 Shared and training-specific transcriptional responses

Two genes were found that were common to all three groups, CET, END and RES, when significant gene sets were compared. Forty-one genes were found to be significant for both CET and END, and four genes were also significant for both CET and RES. The majority of the response was training specific, with 304 genes being specific to CET, 10 to RES, and 7 to END. The reasonably larger overlap of the CET–END was consistent with the inclusion of endurance exercise in both training protocols. This common response included several genes involved with collagen and extracellular matrix. However, as can be seen in the 304 CET-specific genes, concurrent training produced a large transcriptional profile in addition to the genes common to either of the single-mode interventions.

3.6 Functional enrichment of exercise-responsive genes

In total, 127 biological-process terms, 34 molecular-function terms and 26 cellular-component terms were significantly enriched among the differentially expressed genes in the CET. In the END response, 77 biological-process terms, 21 molecular-function terms and 14 cellular-component terms were included. Six biological-

process terms, five molecular-function terms and 10 cellular-component terms were identified in the smaller RES gene set. The most significantly enriched biological process among the 19 genes was collagen fibril organization with an adjusted p-value of 8.863×10^{-16} in CET. 24 genes were identified as significant in the extracellular-matrix organization pathway, and it was also highly enriched (adjusted $p = 6.064 \times 10^{-15}$). The other important processes were cell adhesion, angiogenesis, collagen biosynthesis, cellular response to amino acid stimulus, response to mechanical stimulus, telomere organization, and epigenetic regulation of gene expression. The profile of END was also matrix-like. The 13 genes that were associated with collagen fibril organization yielded an adjusted p-value of 4.445×10^{-20}. There were 15 genes associated with extracellular-matrix organization, with an adjusted p-value of 1.517×10^{-19}. Other processes which were enriched were cell-matrix adhesion, basement-membrane organization, tissue remodeling, collagen biosynthesis, and cellular response to amino acid stimulus. The pattern of enrichment for the RES differed from the matrix-dominated CET and END patterns. LMOD1, MYH1 and MYH6 were involved in muscle contraction, while LMOD1 and MYH6 were involved in myofibril assembly. CFD and C3 were involved in complement activation and alternative pathway activation. The significant enrichment included fatty-acid metabolism and response to bacterium. Leading enriched biological processes for the training groups are shown in Figure 4. Figure 4A reveals that muscle contraction, myofibril assembly, complement activation and fatty-acid metabolism were the features of the RES response. The CET response was dominated by extracellular-matrix organization, collagen organization, cell adhesion, angiogenesis and mechanical-stimulus pathways, as observed in Figure 4B. As seen in Figure 4C, collagen and extracellular-matrix organization, cell-matrix adhesion, basement-membrane organization, and tissue remodeling were characteristics of the END response.

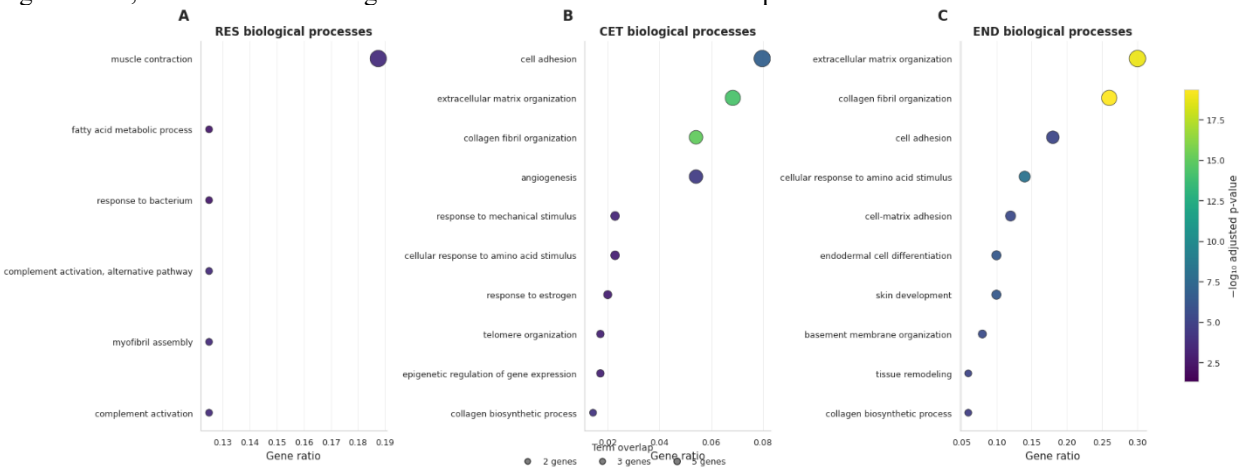

Figure 4. Biological processes enriched after exercise training: (A) leading biological processes following resistance training; (B) leading biological processes following concurrent training; and (C) leading biological processes following endurance training. Point position represents the gene ratio, point size represents the number of overlapping genes, and point color represents $-\log_{10}$ adjusted p-value.

3.7 Gene–phenotype integration

A total of 234 relationships between changes in expression of 26 selected genes and changes in nine physiological outcomes were analysed in the integrated analysis. All p-values were adjusted, and five associations showed unadjusted p-values less than 0.05, but none were significant after false-discovery rate correction. The strongest nominal association was between the change in ELL2 levels and the change in peak oxygen-uptake (Spearman's $\rho = 0.620$, $p = 0.006$, adjusted $p = 0.731$). The expression change of MYH6 significantly correlated with the peak-power improvement in the Wingate test ($\rho = 0.618$, $p = 0.006$, adjusted $p = 0.731$). Negative association was seen between PRSS50 expression and change in leg press ($\rho = -0.518$, $p = 0.028$) and between AQP4 expression and change in peak oxygen-uptake ($\rho = -0.515$, $p = 0.029$); positive association between ELN expression and change in peak oxygen-uptake ($\rho = 0.488$, $p = 0.040$) was seen. None of these relationships was corrected in the 234 tests and was, therefore, considered to be exploratory and not statistically confirmed gene–phenotype associations.

4. DISCUSSION

The training-specific adaptations indicated that there is no single physiological or molecular response to athletic performance. Concurrent training and endurance training resulted in an increase in maximal aerobic power, whereas resistance training resulted in a decrease in maximal aerobic power, with the difference between the interventions being the clearest. It has a very large effect size, and it has a significant Holm-adjusted comparison, which both indicate the specificity of aerobic adaptation. The uncorrected differences in strength on leg press, knee extension, peak oxygen uptake and Wingate power were meaningful but were not so after multiplicity correction. These should hence be interpreted as directional and not as group effects. The different functional responses were not due to different rates of morphological change, as shown by similar increases in lean body mass.

The transcriptomic results showed a greater response to the combined training than to either single-mode training. Of the 351 genes in CET, 50 in END, and 16 in RES. The overall trend of upregulation in the concurrent and endurance groups indicates tissue remodeling activity, while the proportion of downregulated genes in the smaller response seen in the resistance groups indicates the activity of transcription-repressing networks. Depending on the modality, training duration, sampling time and participant characteristics, exercise transcriptomes result in differences in the number and direction of genes showing a response (Pillon et al., 2020). Extracellular-matrix organization and collagen fibril formation dominated the concurrent and endurance signatures. The findings of upregulation of THY1, SFRP2, COL4A1, COL4A2, COL3A1, CPXM1 and the other genes suggest a remodeling response of connective and vascular support structures, rather than simply a response to the contractile fibers. Understanding integrated interpretation of interactions between inherited variation, regulatory state, expression and physiological phenotype is more informative than individual molecular layers in skeletal muscle (Taylor et al., 2019). The 41 genes common to both concurrent and endurance training suggest a remodeling component, whereas 304 genes unique to concurrent training suggest a separate response to the combined stimulus of concurrent training as compared to endurance training.

There were fewer genes found to be significantly different in response to resistance training, but the processes identified were more related to muscle function. The muscle contraction and myofibril assembly pathways showed enrichment of LMOD1, MYH1 and MYH6, and the complement and fatty-acid pathways, metabolic and immune regulation. Typical molecular signatures of strength and power include the contractile, structural, metabolic, and epigenetic mechanisms, which vary in their effects, depending on the biological context (El Haddouchi et al., 2025). There may be genotype–phenotype interactions that affect muscle specialization, which could contribute to the variable molecular and functional responses to similar training stimuli (Flück et al., 2019). Both concurrent and endurance training resulted in increased aerobic capacity, which was accompanied by extracellular-matrix and angiogenic signals, but no gene–phenotype associations were confirmed. The regulation of aerobic capacity and muscle metabolism as a result of cross-interaction between genetic and training factors (Varillas-Delgado, 2024) is illustrated by the regulation of PPARGC1A. However, genomic insights into endurance highlight the interdependence of oxygen transport, mitochondrial control, fuel utilization and recovery, all as aspects of performance (Bottura & Dentillo, 2025). These enrichment results support this systems-level perspective, but the response seen was not limited to metabolic genes, as it also included pathways for structural remodeling. There were no gene–phenotype correlations left after false-discovery-rate correction amongst the 234. The relationships between ELL2, peak oxygen uptake, MYH6 and Wingate power, PRSS50 and leg press strength, and AQP4 or ELN and aerobic adaptation are still hypotheses. They are significantly lower after adjustment and should not be used to come to a strong conclusion about the importance of the genes in a collection. Given the limitations of genotype alone to explain the epigenetic regulation and polygenetic architecture of performance, alongside training history and environmental factors, athlete genetic profiles need to be interpreted (Altynova et al., 2024). These findings are in favour of an integrated approach rather than a genetic approach based on determinism. The results have implications for the exercise adaptation assessment. Functional outcomes showed modality specific outcome and expression patterns showed biological processes that were not observed from body composition alone. Concurrent training retained the aerobic gains and induced tissue remodeling, but it did not yield sufficient uniformity of Wingate response to establish that molecular activity is a sufficient guarantee of uniform performance gains. Combining molecular measurements with performance assessment (Jacques et al., 2025) is supported by multi-omics evidence, as skeletal-muscle adaptation varies depending on the modality of exercise and biological context. This integration could facilitate better identification of adaptive profiles without compromising the physiological responses as the main criteria of training.

There are a few limitations that need to be taken into consideration. The study had a limited number of participants (young men only) and limited generalizability. Only pre and post-training samples were analysed in the transcriptomic approach, leaving aside the assessment of intermediate molecular changes. The exploratory correlations were also not accompanied by a validation sample. Future studies should also involve more varied, larger, and more diverse human cohorts, multiple molecular sampling, and external replication. Combining transcriptomics with other data types, such as genotype, epigenetic, proteomic, and metabolomic, could elucidate the order of the responses that precede the changes in strength, body composition, aerobic fitness, and anaerobic power. This may help guide individual training decisions but without going overboard on the predictive power of any single gene.

5. Conclusion

Physiological/morphological and skeletal-muscle transcriptional adaptations to exercise were different but interrelated. Concurrent training and endurance training resulted in greater gains in aerobic performance, while resistance training resulted in higher gains of strength and anaerobic power. The physiological difference between the training modes was best apparent at maximal aerobic power, and was similar among groups regarding changes in lean body mass. Concurrent training produced the greatest transcriptional response, and endurance training also had significant effects on pathways associated with extracellular-matrix and collagen-remodeling. A smaller, but functionally relevant signature was detected in the context of resistance training and included muscle contraction, myofibril assembly, complement activity and fatty-acid metabolism. However, there is a lack of gene–phenotype correlations that are statistically significant at the false discovery rate level,

suggesting that gene–phenotype associations are not reliably attributable to specific genes alone. Combined evaluation of molecular regulation, muscle function, body composition and training specificity is the most valuable approach to understanding the performance of the athlete. These patterns of responses require validation in larger and more diverse cohorts with multiple molecular samples and multi-omics profiling, to assess their utility for personalized exercise programming.

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