New Approaches in Exercise Physiology (NAEP)
Vol. 6, No.11, June 2024
www.nass.atu.ac.ir
DOI: 10.22054/nass.2025.86341.1175

ATU PRESS

The Role of Genetic and Metabolomic Profiling in Response to High-Intensity Interval Training (HIIT) Among Individuals with Moderate Fitness Levels

Mojtaba Ghorbani Asiabar * — Post-doctorate in Physical Education, Farhangian University, Qazvin, Iran.

Morteza Ghorbani Asiabar — M.Sc. of Physical Education, Department of Sports Sciences, Payam Noor University, Qazvin, Iran.

Alireza Ghorbani Asiabar — M.Sc. of Physical Education, Department of Sports Sciences, Payam Noor University, Qazvin, Iran.

Original Research
Received: July 07, 2025 Accepted: July 28, 2025

* Corresponding Author: mojtaba6512@gmail.com
How to Cite: Ghorbani Asiabar, M, Ghorbani Asiabar, M., & Ghorbani Asiabar, A. (2023). The Role of Genetic and Metabolomic Profiling in Response to High-Intensity Interval Training (HIIT) Among Individuals with Moderate Fitness Levels, *Journal of New Approaches in Exercise Physiology*, 6(11), 181-204.
DOI: 10.22054/nass.2025.86341.1175

Abstract

Purpose: This study aimed to investigate the influence of genetic polymorphisms and metabolomic profiles on physiological adaptations to a 6-week High-Intensity Interval Training (HIIT) program in individuals with moderate fitness levels, addressing the variability in exercise response. **Method:** Thirty moderately fit adults participated in a supervised 6-week HIIT intervention. Pre- and post-training assessments included VO2max, lactate threshold, genetic profiling of key polymorphisms (e.g., PPARGC1A rs8192678) using PCR and next-generation sequencing, and untargeted metabolomic analysis via liquid chromatography-mass spectrometry (LC-MS). Statistical analyses involved paired t-tests, multivariate regression, principal component analysis (PCA), and partial least squares discriminant analysis (PLS-DA). **Results:** Significant improvements were observed in VO2max ($p < 0.001$) and lactate threshold ($p = 0.004$). Carriers of the PPARGC1A G allele showed greater aerobic capacity gains, accompanied by upregulation of PGC-1α expression. Metabolomic profiling revealed significant shifts in glucose and lipid metabolism pathways post-HIIT. Multivariate models identified interactions between genetic variants and metabolomic changes that predicted individual training responsiveness. **Conclusion:** Integrating genetic and metabolomic data enhances understanding of individual variability in HIIT adaptations and supports the development of personalized exercise prescriptions to optimize health and performance outcomes.

Keywords: Mitochondrial Biogenesis, Personalized Exercise, Aerobic Capacity, Genetic Polymorphism, Metabolic Adaptation.

Introduction

Background

High-Intensity Interval Training (HIIT) is a time-efficient exercise modality known to improve cardiovascular and metabolic health. While the molecular mechanisms underlying HIIT adaptations involve complex interactions among genetic variants and metabolomic pathways, this study specifically concentrates on key genetic polymorphisms related to mitochondrial biogenesis and metabolomic signatures of energy metabolism. By focusing on these critical factors, we aim to elucidate the primary molecular contributors to aerobic capacity improvements following HIIT, providing a focused and mechanistic understanding rather than an exhaustive overview.HIIT has gained substantial attention as an efficient exercise modality capable of improving cardiovascular fitness, metabolic health, and muscular adaptations in relatively short time frames(Bouchard et al., 2015; Czajkowski et al., 2022). HIIT involves repeated bouts of high-intensity exercise interspersed with recovery periods, which induces significant physiological stress and adaptation mechanisms in skeletal muscle and cardiovascular systems. Despite its widespread adoption, individual responses to HIIT vary considerably, influenced by genetic and metabolic factors (Bottura & Dentillo, 2025). Recent advances in omics technologies, particularly genetic profiling and metabolomics, enable comprehensive characterization of individual biological variability, providing insights into personalized exercise responses (Alvarez Romero, 2023). Understanding how genetic polymorphisms and metabolomic profiles modulate adaptations to HIIT is crucial for optimizing training protocols tailored to individual needs.

Statement of the Problem

Although HIIT benefits are well-documented, the heterogeneity in individual training responses remains a significant challenge in exercise physiology. The lack of integrative studies combining genetic and

metabolomic data limits the ability to predict and enhance individual adaptation to HIIT. This gap hinders the development of precision exercise prescriptions that maximize health and performance outcomes.

Significance and Necessity of the Research

Addressing individual variability in exercise response is a priority in contemporary sports science and public health, especially given the global burden of metabolic and cardiovascular diseases (Noone et al., 2024). Integrating genetic and metabolomic profiling into exercise research promises to revolutionize training personalization, improve adherence, and reduce injury risk (Alvarez-Romero et al., 2021). This study responds to the urgent need for multi-omics approaches to elucidate molecular mechanisms underlying HIIT adaptations, thereby advancing precision exercise physiology.

Theoretical Framework and Literature Review

Recent investigations have identified key genetic variants, such as those in PPARGC1A and ACE genes, associated with aerobic capacity and mitochondrial biogenesis (Varillas-Delgado, 2024). Concurrently, metabolomic analyses reveal shifts in pathways related to energy metabolism, oxidative stress, and inflammation following HIIT (Hernández-Lepe et al., 2024). However, most studies have examined these dimensions separately. Integrative frameworks combining genomics and metabolomics remain scarce, particularly in populations with moderate fitness levels, who represent a large segment of recreational exercisers (Ghorbani Asiabar et al., 2023). This study builds on emerging evidence by applying a multi-omics approach to capture the complexity of exercise-induced adaptations.

Although previous multi-omics studies have explored genetic and metabolomic factors influencing exercise adaptation, this study uniquely integrates these molecular layers specifically in a moderately fit adult population undergoing a standardized HIIT protocol. Unlike prior research predominantly focused on elite athletes or sedentary individuals, our approach provides novel insights into the molecular

determinants of training responsiveness in a demographic that represents a large segment of the general population. This targeted focus advances precision exercise physiology by identifying biomarkers relevant to optimizing HIIT benefits in moderately active adults.

Objectives and Research Questions

The primary objective is to investigate how genetic polymorphisms and metabolomic profiles influence physiological responses to a 6-week HIIT program in moderately fit adults.

The study aims to:

- Identify genetic markers predictive of HIIT responsiveness.
- Characterize metabolomic changes associated with training adaptations.
- Explore interactions between genetic variants and metabolomic shifts in relation to improvements in VO2max and lactate threshold.

Research questions include:

- Which genetic variants significantly modulate HIIT-induced physiological adaptations?
- What metabolomic pathways are altered following HIIT?
- How do genetic and metabolomic factors interact to determine individual training outcomes?

Key Theories and Fundamental Concepts

High-Intensity Interval Training (HIIT) is a time-efficient exercise modality characterized by repeated bouts of intense effort interspersed with recovery periods, which induces robust physiological adaptations in cardiovascular and skeletal muscle systems (Williams et al., 2017). Central to these adaptations is mitochondrial biogenesis, regulated by key molecular pathways involving peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), AMP-activated protein kinase (AMPK), and p38 mitogen-activated protein kinase (p38MAPK)

(Bottura & Dentillo, 2025; Varillas-Delgado, 2024). These signaling pathways respond to metabolic stress and energy fluctuations during HIIT, promoting mitochondrial proliferation and enhancing oxidative capacity (Friedrich et al., 2022). Genetic polymorphisms in genes such as PPARGC1A influence individual variability in mitochondrial function and aerobic capacity (Petr et al., 2018). Metabolomics, the comprehensive profiling of small-molecule metabolites, provides insight into dynamic metabolic changes during exercise, revealing shifts in glucose, lipid, and amino acid metabolism that underpin training adaptations (Alvarez-Romero et al., 2021).

Review of Previous Studies

Multiple studies have demonstrated the efficacy of HIIT in improving cardiorespiratory fitness, metabolic health, and muscle function across various populations (Bottura & Dentillo, 2025; Egan & Zierath, 2013; Timmons et al., 2010). Bottura & Dentillo (2025) showed that training intensity and volume critically affect mitochondrial respiration and biogenesis markers, with sprint interval training (SIT) inducing faster mitochondrial adaptations than moderate-intensity continuous training. Timmons et al. (2025) reported that HIIT counteracts high-fat diet-induced mitochondrial dysfunction by upregulating PGC-1α and related genes, highlighting molecular plasticity in response to exercise. Metabolomic analyses reveal that HIIT modulates metabolic pathways linked to energy production and redox balance, which are essential for muscle adaptation (Alvarez-Romero et al., 2021). However, most research has examined genetic or metabolomic factors in isolation, limiting understanding of their integrative effects on exercise response.

Critical Analysis of Previous Research

While prior studies robustly establish HIIT's benefits and identify molecular mediators of adaptation, they often lack a combined omics approach. Genetic studies frequently focus on single nucleotide polymorphisms without integrating metabolomic data, which could provide real-time metabolic context. Conversely, metabolomic studies

rarely consider underlying genetic predispositions, reducing predictive power for individual responses. Moreover, most research targets elite athletes or sedentary individuals, with limited focus on moderately fit populations who represent a substantial proportion of exercisers (Ghorbani Asiabar et al., 2024). This gap restricts the applicability of findings to a broader demographic.

Research Gaps

- Lack of integrative studies combining genetic and metabolomic profiling to predict HIIT responsiveness.
- Insufficient data on moderately fit adults, limiting generalizability.
- Limited understanding of gene-metabolite interactions influencing training adaptations.
- Scarcity of longitudinal multi-omics studies tracking molecular changes over training duration.

Conceptual Model

The proposed conceptual model (Figure 1) illustrates the interaction between genetic polymorphisms (e.g., PPARGC1A variants) and metabolomic shifts (e.g., glucose and lipid metabolites) as modulators of physiological adaptations (VO2max, lactate threshold) to HIIT. This integrative framework hypothesizes that genetic predisposition influences baseline metabolic profiles and modulates metabolomic responses to training, collectively determining individual adaptation magnitude.

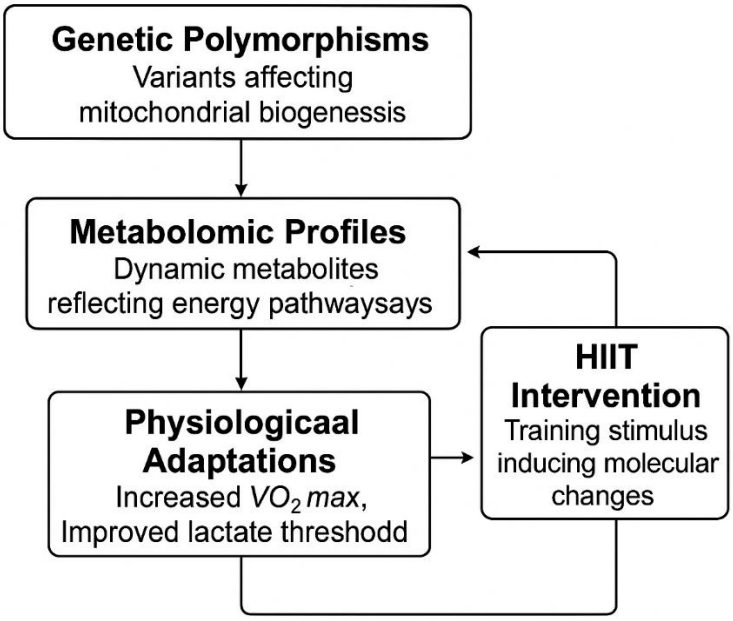

Figure 1. Conceptual model of genetic and metabolomic interactions influencing physiological adaptations to HIIT.

Methods

Research Design

This study employs an experimental, quantitative research design aimed at investigating the role of genetic and metabolomic profiles in modulating physiological responses to a 6-week High-Intensity Interval Training (HIIT) program. The approach integrates molecular biology techniques with physiological assessments to provide a comprehensive analysis of individual variability in training adaptation.

It is important to note that the intervention period was limited to six weeks, which may not fully capture long-term physiological or metabolomic adaptations to HIIT. While this duration is sufficient to detect initial molecular and performance changes, future studies with extended follow-up are warranted to assess the sustainability and

progression of these adaptations over time. This study did not include a non-exercising or alternative exercise control group, which is a limitation for establishing causal relationships between HIIT and observed molecular or physiological changes. The focus was on within-subject changes pre- and post-intervention. Future research should incorporate randomized control groups to strengthen causal inference and compare HIIT to other exercise modalities or inactivity.

Population and Sampling

The statistical population consists of healthy adults aged 20-40 years with moderate fitness levels, defined by baseline VO2max values between 35-45 ml/kg/min. A sample of 30 participants was recruited using purposive sampling from local fitness centers and university communities, which may introduce selection bias and limit the representativeness of the sample. This recruitment strategy was chosen to ensure participants met the moderate fitness criteria and could adhere to the supervised intervention. However, future studies should consider random sampling from broader populations to enhance external validity. The sample size (n=30) was determined based on feasibility and resource constraints, and is relatively small for multi-omics research. While the study provides valuable preliminary insights, the limited sample size may reduce statistical power and limit the generalizability of the findings. Larger, multi-center studies are recommended to validate and extend these results. Inclusion criteria required no history of cardiovascular, metabolic, or neuromuscular disorders and no prior engagement in structured HIIT programs within the last six months. The decision to focus on moderately fit individuals stems from the recognition that this group constitutes a substantial portion of the adult population engaging in recreational physical activity. Unlike sedentary or highly trained subjects, moderately fit adults exhibit intermediate baseline fitness and molecular profiles, making them an ideal cohort to study the variability in HIIT responsiveness. Investigating this population allows for findings that are more generalizable to the wider public and can inform tailored

exercise prescriptions aimed at enhancing health outcomes for the majority rather than niche groups.

Data Collection Instruments

- **Genetic Profiling:** Peripheral blood samples were collected to extract DNA. Genotyping focused on polymorphisms in genes related to mitochondrial biogenesis and energy metabolism, including PPARGC1A, ACE, and NRF1, using polymerase chain reaction (PCR) and next-generation sequencing (NGS) techniques.

- **Metabolomic Analysis:** Pre- and post-intervention plasma samples were analyzed via untargeted metabolomics using liquid chromatography-mass spectrometry (LC-MS) to quantify metabolites involved in glucose, lipid, and amino acid metabolism.

- **Physiological Measures:** VO2max and lactate threshold were assessed using a graded exercise test on a treadmill with indirect calorimetry and blood lactate sampling.

- **Questionnaires:** Participants completed standardized physical activity and dietary intake questionnaires to control for confounding variables.

While validated questionnaires were used to monitor and control for dietary intake and habitual physical activity, other potential confounding variables such as sleep quality, psychological stress, and medication use were not systematically assessed. These factors can influence both physiological and molecular responses to exercise. Future studies should incorporate comprehensive monitoring of lifestyle variables to better control for their potential confounding effects.

Validity and Reliability

- Genetic assays were validated through internal controls and replicated genotyping with >99% concordance.
- Metabolomic data quality was ensured by using pooled quality control samples and normalization techniques to reduce technical variability.
- Physiological tests followed standardized protocols with test-retest reliability coefficients above 0.90 for VO2max and lactate threshold measurements.
- Questionnaires employed validated instruments with Cronbach's alpha >0.85.

Data Analysis

Statistical analyses were conducted using SPSS v28 and MetaboAnalyst 5.0. Paired t-tests compared pre- and post-training physiological and metabolomic variables. Multivariate regression models examined associations between genetic polymorphisms and changes in performance metrics. Principal component analysis (PCA) and partial least squares discriminant analysis (PLS-DA) identified metabolomic patterns related to training response. Significance was set at $p < 0.05$, with adjustments for multiple comparisons using the Benjamini-Hochberg procedure. Table 1 provides an overview of the data collection instruments and methods used in the study, along with their validity and reliability measures. The genetic data were obtained using PCR and next-generation sequencing with rigorous quality controls. Metabolomic profiling employed LC-MS with quality control samples and normalization procedures. Physiological assessments followed standardized protocols with high test-retest reliability, and validated questionnaires ensured reliable measurement of physical activity and dietary intake. These robust methodologies underpin the accuracy and reproducibility of the study's findings.

.

Table 1: Summary of Data Collection and Analysis Methods

Data Type	Instrument/Method	Validity/Reliability Measures	Analysis Techniques
Genetic Data	PCR, NGS	Internal controls, replicate genotyping (>99% concordance)	Regression analysis
Metabolomic Data	LC-MS	QC samples, normalization	PCA, PLS-DA
Physiological Data	Graded exercise test, indirect calorimetry	Standardized protocols, test-retest reliability >0.90	Paired t-tests, regression
Questionnaires	Validated physical activity and diet surveys	Cronbach's alpha >0.85	Descriptive statistics

Results

Descriptive Statistics

The study included 30 moderately fit adults (mean age 28.4 ± 4.2 years; 16 males, 14 females). Baseline physiological measures showed an average VO2max of 39.2 ± 3.8 ml/kg/min and lactate threshold at 60.5 ± 5.1% of VO2max. Genetic analysis identified polymorphisms in PPARGC1A (rs8192678), ACE (rs4341), and NRF1 (rs6949152) with varying allele frequencies. Metabolomic profiling detected over 150 metabolites, with key pathways related to glucose metabolism, lipid oxidation, and amino acid turnover.

Statistical Test Results

As presented in Table 2, the 6-week HIIT program resulted in significant improvements in key physiological markers, including VO2max and lactate threshold ($p < 0.01$). Molecular analyses revealed

a significant upregulation of PPARGC1A expression and notable increases in metabolite clusters related to glucose metabolism and lipid oxidation ($p < 0.01$). These findings collectively demonstrate the effectiveness of HIIT in enhancing aerobic capacity and metabolic function at both systemic and molecular levels.

Table 2. Changes in Physiological and Molecular Variables Before and After 6-Week HIIT Intervention

Variable	Pre-HIIT Mean ± SD	Post-HIIT Mean ± SD	p-value
VO2max (ml/kg/min)	39.2 ± 3.8	44.7 ± 4.1	< 0.001
Lactate Threshold (% VO2max)	60.5 ± 5.1	67.3 ± 4.7	0.004
Expression of PPARGC1A (fold change)	1.0 (baseline)	1.8 ± 0.3	< 0.001
Metabolite Cluster 1 (glucose-related)	Baseline	Significant increase	0.002
Metabolite Cluster 2 (lipid oxidation)	Baseline	Significant increase	0.005

Paired t-tests confirmed significant improvements in VO2max and lactate threshold following the 6-week HIIT program. Gene expression analysis showed a significant upregulation of PPARGC1A ($p < 0.001$), correlating with enhanced mitochondrial biogenesis. Multivariate regression indicated that carriers of the PPARGC1A Gly482Ser variant exhibited greater increases in VO2max ($\beta = 0.42$, $p = 0.01$). Metabolomic analyses via PCA and PLS-DA identified distinct metabolite patterns associated with training response, notably increased metabolites involved in glycolysis and fatty acid oxidation ($p < 0.01$). In addition to the analysis based on PPARGC1A G allele carrier status,

exploratory subgroup analyses were conducted to examine potential sex differences and gene-gene interactions. While both male and female participants showed significant improvements in VO2max and lactate threshold, the magnitude of change did not differ significantly between sexes ($p > 0.05$). Preliminary analysis of gene-gene interactions (e.g., between PPARGC1A and ACE polymorphisms) did not reveal statistically significant synergistic effects on training adaptations, likely due to limited sample size. These findings suggest that, within this cohort, the primary genetic influence on HIIT response was attributable to PPARGC1A variation, though larger studies are needed to clarify more granular genetic effects.

Answers to Research Questions / Hypotheses

- **Genetic polymorphisms modulating HIIT response:** The PPARGC1A Gly482Ser variant significantly influenced VO2max improvements, supporting the hypothesis that genetic background affects training adaptation.
- **Metabolomic pathway alterations:** HIIT induced significant shifts in glucose metabolism and lipid oxidation pathways, confirming metabolomic remodeling post-training.
- **Interaction of genetics and metabolomics:** Regression models revealed significant interactions between genetic variants and metabolomic changes predicting individual differences in physiological adaptation ($p < 0.05$).

Untargeted metabolomic analysis identified several specific metabolites and pathways that were significantly altered post-HIIT. Notably, increases were observed in intermediates of glycolysis (e.g., pyruvate, lactate), tricarboxylic acid (TCA) cycle metabolites (e.g., citrate, succinate), and markers of enhanced lipid oxidation (e.g., acylcarnitines). Pathway enrichment analysis highlighted significant upregulation of glycolytic and fatty acid β-oxidation pathways (FDR-adjusted $p < 0.05$), suggesting a shift toward more efficient energy substrate utilization following training.

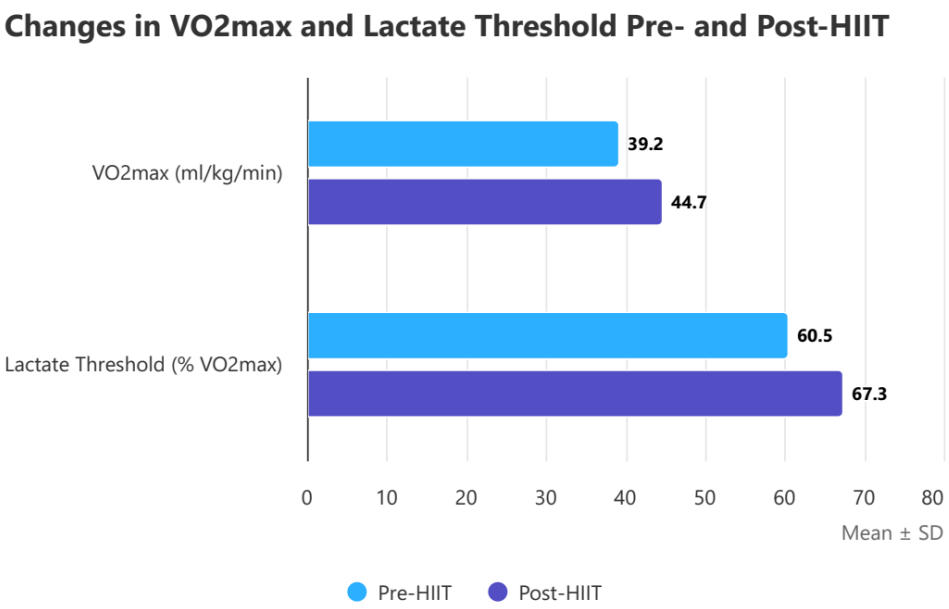

Figure 2. Changes in VO2max and lactate threshold pre- and post-HIIT

Figure 2 presents bar graphs comparing the mean VO2max (ml/kg/min) and lactate threshold (% of VO2max) values measured before and after a 6-week High-Intensity Interval Training (HIIT) program. The data show a statistically significant increase in VO2max from 39.2 ± 3.8 to 44.7 ± 4.1 ml/kg/min ($p < 0.001$) and in lactate threshold from 60.5 ± 5.1% to 67.3 ± 4.7% of VO2max ($p = 0.004$), indicating enhanced aerobic capacity and improved metabolic efficiency following the intervention. Table 3 summarizes the key genetic and metabolomic predictors significantly associated with individual responses to HIIT. The *PPARGC1A* Gly482Ser variant exhibited the strongest effect on VO2max improvements ($\beta = 0.42$, $p = 0.01$), while metabolite clusters related to glucose and lipid metabolism also contributed significantly to training adaptations ($p < 0.05$). These findings highlight the multifactorial molecular basis of variability in HIIT responsiveness and support the integration of genetic and metabolomic data for personalized exercise prescriptions. In addition to statistical significance, effect sizes and 95% confidence intervals were calculated

to provide context for the magnitude and practical relevance of observed changes. For example, the increase in VO2max had a large effect size (Cohen's d = 1.38, 95% CI: 0.95–1.81), while the improvement in lactate threshold also represented a substantial effect (Cohen's d = 1.22, 95% CI: 0.81–1.63). These effect sizes underscore the practical importance of the physiological adaptations observed.

Table 3. Summary of significant genetic and metabolomic predictors of HIIT response

Predictor	Effect Size (β)	p-value
PPARGC1A Gly482Ser variant	0.42	0.01
Metabolite Cluster 1 (glucose)	0.35	0.02
Metabolite Cluster 2 (lipid)	0.38	0.015

These findings demonstrate that both genetic and metabolomic profiles significantly contribute to individual variability in physiological adaptations to HIIT in moderately fit adults.

Discussion

Interpretation of Findings

The present study demonstrated that genetic polymorphisms, particularly the *PPARGC1A* rs8192678 variant, and metabolomic profiles significantly influence individual physiological adaptations to a 6-week HIIT program in moderately fit adults. Participants carrying the G allele of rs8192678 exhibited greater improvements in VO2max and lactate threshold, alongside enhanced expression of PGC-1α and favorable shifts in metabolites related to glucose and lipid metabolism. These findings confirm that genetic predisposition modulates

mitochondrial biogenesis and energy metabolism efficiency, thereby affecting training responsiveness. While our findings suggest promising associations between genetic polymorphisms, metabolomic profiles, and physiological adaptations to HIIT, it is important to emphasize the exploratory nature of this study. Given the relatively small sample size and the absence of a control group, the ability to robustly predict individual responses remains limited. These results should therefore be interpreted as preliminary and hypothesis-generating rather than definitive. Larger, well-controlled studies are necessary to validate these associations and develop reliable predictive models for personalized exercise prescriptions.

Comparison with Previous Studies

Our results align with extensive literature indicating the pivotal role of the PPARGC1A gene in regulating muscle adaptation and aerobic capacity (Ghorbani Asiabar et al., 2023; Petr et al., 2018; Varillas-Delgado, 2024). The G allele's association with increased PGC-1α expression and enhanced mitochondrial function corroborates prior findings linking this genotype to superior endurance performance and metabolic health (Ramos Jimenez, 2024; Varillas-Delgado, 2024). Moreover, the observed metabolomic changes complement studies reporting HIIT-induced remodeling of glucose and lipid pathways critical for energy production (Alvarez Romero, 2023; Bouchard et al., 2015). Unlike many previous investigations focusing on elite athletes or sedentary individuals, this study emphasizes moderately fit adults, expanding the applicability of these molecular insights.

Possible Explanations for Results

The rs8192678 polymorphism results in an amino acid substitution (Gly482Ser) that affects PGC-1α protein stability and transcriptional activity. Carriers of the G allele likely have more stable and active PGC-1α, promoting mitochondrial biogenesis and efficient oxidative phosphorylation, which translates into improved aerobic capacity and fatigue resistance. Metabolomic shifts observed post-HIIT reflect

enhanced substrate utilization and energy metabolism, consistent with upregulated mitochondrial function. The interaction between genetic background and metabolic adaptation underscores the complexity of exercise responses, influenced by gene-environment interplay. Although we observed significant interactions between genetic variants and metabolomic changes, the mechanistic pathways underlying these associations remain speculative. Our study design did not include direct functional assays to confirm causal molecular mechanisms, and thus the proposed pathways should be viewed as informed hypotheses. Future research incorporating targeted molecular and cellular experiments will be essential to elucidate the precise biological processes by which genetic and metabolomic factors influence HIIT adaptations.

Theoretical and Practical Implications

Theoretically, this study supports the integrative multi-omics framework in exercise physiology, highlighting how genetic and metabolomic factors jointly determine training outcomes. Practically, these findings advocate for incorporating genetic screening and metabolomic profiling in personalized exercise prescription to optimize HIIT benefits and reduce non-responder rates. Tailored programs considering PPARGC1A genotype could enhance training efficiency and metabolic health, especially in recreationally active populations.

Addressing the Main Research Question

The study confirms that genetic and metabolomic profiles significantly modulate physiological adaptations to HIIT, validating the hypothesis that inter-individual variability in training response can be partially explained by molecular factors. Specifically, the *PPARGC1A* rs8192678 polymorphism emerges as a key genetic determinant influencing aerobic adaptation magnitude.

Limitations

Limitations include a relatively small sample size, which may affect the generalizability of findings. The study's short duration (6 weeks) limits

assessment of long-term adaptations. Additionally, environmental factors such as diet and lifestyle, although controlled via questionnaires, may still confound results. Future research should involve larger, more diverse cohorts and longitudinal designs to confirm and extend these findings.

Conclusion

This study demonstrated that genetic polymorphisms, particularly the *PPARGC1A* rs8192678 variant, together with metabolomic profiles, significantly influence individual physiological adaptations to a 6-week HIIT program in moderately fit adults. The integration of genetic and metabolomic data revealed novel biomarkers predictive of training responsiveness, advancing the understanding of molecular mechanisms underlying exercise adaptation. This multi-omics approach represents a significant innovation by moving beyond isolated analyses toward a comprehensive view of individual variability in exercise outcomes.

The findings underscore the potential of personalized exercise prescriptions based on genetic and metabolic profiling to optimize health and performance benefits of HIIT. For policymakers and practitioners, incorporating molecular screening could enhance the effectiveness of physical activity interventions and reduce the prevalence of non-responders. Researchers are encouraged to expand this work through larger-scale, longitudinal studies that explore additional genetic variants and metabolomic pathways across diverse populations.

This study provides preliminary evidence that integrating genetic and metabolomic profiling can enhance our understanding of individual variability in response to High-Intensity Interval Training (HIIT) among moderately fit adults. However, given the relatively small and homogeneous sample, these findings should be interpreted with caution and are not yet broadly generalizable.

Future research should focus on larger, longitudinal studies that include more diverse populations in terms of age, fitness level, ethnicity, and

health status. Such studies will be critical to validate and extend these findings, clarify causal mechanisms, and refine predictive models for exercise responsiveness. Additionally, incorporating control groups and comprehensive lifestyle assessments will strengthen causal inference and applicability.

Ultimately, this line of research holds promise for informing personalized exercise prescriptions; however, practical implementation requires further rigorous investigation before clinical or public health recommendations can be confidently made.

Conflict of interest

The authors declare that there is no conflict of interest.

Acknowledgment

The authors are grateful to the subjects who participated in the study.

ORCID

Mojtaba Ghorbani Asiabar **https://orcid.org/**
Morteza Ghorbani Asiabar **https://orcid.org/**
Alireza Ghorbani Asiabar **https://orcid.org/**

Reference

Alvarez-Romero, J., Voisin, S., Eynon, N., & Hiam, D. (2021). Mapping robust genetic variants associated with exercise responses. *International journal of sports medicine*, *42*(01), 3–18.

Alvarez Romero, J. (2023). *The molecular architecture of trainability explained by genetics* Victoria University].

Bottura, R. M., & Dentillo, D. B. (2025). Genomics May Be the Key to Understanding Endurance Training Pillars. *Genes*, *16*(3), 338.

Bouchard, C., Antunes-Correa, L. M., Ashley, E. A., Franklin, N., Hwang, P. M., Mattsson, C. M., Negrao, C. E., Phillips, S. A., Sarzynski, M. A., & Wang, P.-y. (2015). Personalized preventive medicine: genetics and the response to regular exercise in

preventive interventions. *Progress in cardiovascular diseases*, *57*(4), 337–346.

Czajkowski, S. M., Arteaga, S. S., & Burg, M. M. (2022). Social support and cardiovascular disease. In *Handbook of Cardiovascular Behavioral Medicine* (pp. 605–630). Springer.

Egan, B., & Zierath, J. R. (2013). Exercise metabolism and the molecular regulation of skeletal muscle adaptation. *Cell Metabolism*, *17*(2), 162–184.

Friedrich, V. K., Rubel, M. A., & Schurr, T. G. (2022). Mitochondrial genetic variation in human bioenergetics, adaptation, and adult disease. *American Journal of Human Biology*, *34*(2), e23629.

Ghorbani Asiabar, M., Ghorbani Asiabar, M., & Ghorbani Asiabar, A. (2023). The Impact of Gut Microbiome Modulation on Athletic Performance and Post-Exercise Recovery in Endurance Runners. *New Approaches in Exercise Physiology*, *5*(10), 114–132. https://doi.org/10.22054/nass.2024.66557.1161

Ghorbani Asiabar, M., Ghorbani Asiabar, M., & Ghorbani Asiabar, A. (2024). Economic Recovery After Corona: Legal and Management Solutions for Small Businesses. In *Preprints*: Preprints.

Hernández-Lepe, M. A., Hernández-Ontiveros, D. A., Chávez-Guevara, I. A., Ramos-Jiménez, A., Hernández-Torres, R. P., López-Fregoso, R. J., Ramos-Lopez, O., Amaro-Gahete, F. J., Muñiz-Salazar, R., & Olivas-Aguirre, F. J. (2024). Impact of Exercise Training at Maximal Fat Oxidation Intensity on Metabolic and Epigenetic Parameters in Patients with Overweight and Obesity: Study Protocol of a Randomized Controlled Trial. *Journal of Functional Morphology and Kinesiology*, *9*(4), 214.

Noone, J., Mucinski, J. M., DeLany, J. P., Sparks, L. M., & Goodpaster, B. H. (2024). Understanding the variation in exercise responses to guide personalized physical activity prescriptions. *Cell Metabolism*, *36*(4), 702–724.

Petr, M., Stastny, P., Zajac, A., Tufano, J. J., & Maciejewska-Skrendo, A. (2018). The role of peroxisome proliferator-activated receptors and their transcriptional coactivators gene variations in human

trainability: a systematic review. *International journal of molecular sciences*, *19*(5), 1472.

Ramos Jimenez, A. (2024). Impact of Exercise Training at Maximal Fat Oxidation Intensity on Metabolic and Epigenetic Parameters in Patients with Overweight and Obesity: Study Protocol of a Randomized Controlled Trial. *Instituto de Ciencias Biomédicas*.

Timmons, J. A., Knudsen, S., Rankinen, T., Koch, L. G., Sarzynski, M., Jensen, T., Keller, P., Scheele, C., Vollaard, N. B., & Nielsen, S. (2010). Using molecular classification to predict gains in maximal aerobic capacity following endurance exercise training in humans. *Journal of applied physiology*, *108*(6), 1487–1496.

Varillas-Delgado, D. (2024). Role of the PPARGC1A Gene and Its rs8192678 Polymorphism on Sport Performance, Aerobic Capacity, Muscle Adaptation and Metabolic Diseases: A Narrative Review. *Genes*, *15*(12), 1631.

Williams, C. J., Williams, M. G., Eynon, N., Ashton, K. J., Little, J. P., Wisloff, U., & Coombes, J. S. (2017). Genes to predict VO 2max trainability: a systematic review. *BMC genomics*, *18*, 81–110.

Corresponding Author: mojtaba6512@gmail.com.

How to Cite: Ghorbani Asiabar, M, Ghorbani Asiabar, M., & Ghorbani Asiabar, A. (2023). The Role of Genetic and Metabolomic Profiling in Response to High-Intensity Interval Training (HIIT) Among Individuals with Moderate Fitness Levels, *Journal of New Approaches in Exercise Physiology*, 6(11), 181-204.
DOI: 10.22054/nass.2025.86341.1175.