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Posted Date: 22 October 2024

doi: 10.20944/preprints202410.1705.v1

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Article

Socceromics: The Integration of Omics Technologies in Soccer to Enhance Performance and Health. A Comprehensive, Critical Review of the Literature

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Abstract: The integration of omics technologies, including genomics, metabolomics, proteomics, and microbiomics, has transformed sports science, particularly in soccer, where these advancements have the potential to enhance player performance, injury prevention, and recovery. This review examines the role of single nucleotide polymorphisms (SNPs) across key genes influencing various physiological traits crucial for elite soccer players. Genes related to the cardiovascular system (ACE, AGT, NOS3, VEGF), muscle structure and function (ACTN3, CKM, MLCK), neurotransmission (ADRA2A, ADRB2, BDNF, DRD1, DBH), connective tissue integrity (COL1A1, COL2A1, COL5A1, ELN, EMILIN1, TNC), energy metabolism (AMPD1, MCT1, UCP1/2/3), oxidative stress response (GSTM1, GSTP, GSTT), hormonal regulation (CYP2D6, HSD17B14), and growth factors (GDF-8, IGF2, HGF) are all highlighted for their roles in influencing soccer-specific traits like endurance, speed, and injury risk. Furthermore, the incorporation of omics data allows for personalized strategies in training, nutrition, and recovery, tailoring interventions to each player's genetic and biochemical profile. For example, genomic markers such as ACE I/D and ACTN3 R577X are linked to key athletic traits like endurance and muscle injury susceptibility, while proteomics sheds light on muscle repair mechanisms, and metabolomics provides real-time insights into energy metabolism and fatigue markers. Microbiomics explores the role of gut health in recovery and overall performance, revealing correlations between microbial diversity and enhanced athletic outcomes. This comprehensive approach, referred to as Socceromics, offers a more holistic understanding of an athlete's health and performance capabilities. Integrating these findings into real-world applications is essential for optimizing training regimens and reducing injury risk, ultimately pushing the boundaries of what athletes can achieve on the field. Future research should focus on expanding the scope of omics integration and improving the generalizability of findings across diverse populations and genders, thus advancing the field of precision sports medicine.

Keywords: soccer; omics technologies; genomics; proteomics; metabolomics; microbiomics; integrative omics; sportomics; athlomics; socceromics

 doi:10.20944/preprints202410.1705.v1

1. Introduction

Soccer is among the most physically demanding sports, requiring not only peak physical fitness but also advanced mental and tactical skills [1,2]. A typical 90-minute match sees elite players cover approximately 10 kilometers [2]. This high-level cardiovascular demand illustrates the balance between endurance and high-intensity bursts that players must maintain throughout the game. Soccer involves diverse physical activities like sprinting, tackling, and jumping, which push players to exert energy in multiple forms. Sprinting requires explosive power and speed, while tackling and jumping place demands on muscular strength, coordination, and agility [3,4]. These high-intensity efforts are typically interspersed with periods of lower-intensity movement like jogging or walking, allowing players to recover momentarily before re-engaging at a high level of intensity.

In addition to physical endurance and strength, players must maintain sharp mental focus and tactical awareness. Decision-making, anticipation, and positioning are critical to adapting to the flow of the game, as teams constantly switch between offensive and defensive phases. This mental acuity is essential for successfully executing strategies and reacting to opponents' actions under conditions of physical fatigue. Soccer's demands on both aerobic and anaerobic energy systems highlight the complexity of training programs for athletes, which must address endurance, strength, speed, and mental resilience. Players also need tactical training that helps them make quick decisions while maintaining high physical performance, leading to a game that tests an athlete's holistic capacity for both physical and cognitive excellence [5].

With advancements in sports science, the use of omics technologies—such as genomics, metabolomics, proteomics, and microbiomics—has gained significant attention in soccer due to their ability to provide a comprehensive understanding of an athlete's physiological state. These technologies offer insights into how genetic, molecular, and biochemical profiles can influence a variety of outcomes, including performance, injury risk, recovery, and adaptation to training [6–10].

Socceromics, as we define it, refers to the integration of these omics technologies in soccer to enhance performance and health. This paradigm shift toward personalized and data-driven interventions offers clubs a unique opportunity to tailor strategies to individual players' physiological profiles, thereby improving outcomes both on and off the pitch.

2. Material and Methods

2.1. Search Strategy

We conducted a comprehensive search across multiple databases, including MEDLINE via PubMed, Scopus, and ISI/Web of Science (WoS), for articles published up to September 9, 2024. The search strategy utilized a combination of keywords and MeSH terms relevant to omics technologies and soccer, including: soccer, football, genomics, polymorphisms, genetic variants, metabolomics, metabolites, microbiome, microbiota, methylome, methylomics, epigenomics, sportomics, and athlomics.

2.2. Inclusion and Exclusion Criteria

Studies were included if they met the following criteria: i) peer-reviewed articles related to omics technologies in soccer, ii) studies that included athletes at the professional or elite level, and iii) articles focused on the use and/or integration of genomics, metabolomics, proteomics, or microbiomics in enhancing performance, injury prevention, or recovery in soccer players.

Studies were excluded if they: i) were not written in English, ii) did not involve human participants, iii) focused on other sports than soccer (such as American or Australian football), and iv) focused exclusively on non-omics approaches, such as traditional physiological studies without molecular data.

2.3. Data Extraction

 doi:10.20944/preprints202410.1705.v1

Data extraction focused on capturing key information related to study design, participant characteristics, sample collection methods, and omics technologies used. Extracted data included: i) sample sizes and populations (e.g., professional soccer players, elite athletes), ii) type of omics analysis (e.g., genomics, proteomics, metabolomics, microbiomics), iii) specific markers or genes studied (e.g., ACTN3, COL1A1, metabolic biomarkers), iv) results, including associations between omics data and performance, injury risk, or recovery times, and v) methodological limitations noted in the studies.

2.4. Data Synthesis

Data from the included studies were synthesized in a narrative format, categorizing findings according to each omics technology: genomics, metabolomics, proteomics, and microbiomics.

3. Results

3.1. Genomics in Soccer

Genomic profiling is rapidly becoming an essential tool in sports science, helping to predict and enhance performance while minimizing injury risk [11–16]. The study of genetic polymorphisms has demonstrated that certain genetic variants can influence key athletic traits as well as predispose to injuries (Table 1).

Table 1. An overview of the Single Nucleotide Polymorphsism associated with performance and injury risk in soccer players.

Gene	Polymorphism	Associated Trait	Study Findings
Cardiovascular System-Related Polymorphisms			
ACE	I/D	Endurance, strength, hypertrophy	The I allele is associated with endurance, while the D allele is linked to strength and hypertrophy ACE polymorphisms influence left ventricular mass and muscle injury
AGT	rs699	Blood pressure, athletic performance	Associated with regulation of blood pressure and electrolyte balance Contradictory findings regarding performance and hemodynamic responses
NOS3	-786 T/C, Glu298Asp	Endurance, strength	C allele associated with reduced nitric

 doi:10.20944/preprints202410.1705.v1

			oxide production and potential injury protection. NOS3 polymorphisms influence positional predispositions
VEGF	rs2010963	Endurance, vascularization, recovery	Enhances oxygen transport and accelerates recovery through improved vascularization and tissue regeneration
Muscle Structure and Function-Related Polymorphisms			
ACTN3	R577X	Speed, muscle injury risk	Players with the RR genotype have greater speed and power. XX genotype is associated with higher injury susceptibility.
CKM	rs8111989	Muscle metabolism, injury risk	Influences muscle energy metabolism and recovery. GG genotype linked to higher frequency of muscle contractures.
MLCK	Various SNPs	Muscle contraction, injury risk	Associated with muscle contraction and force generation. MLCK variants are linked to muscle injuries in soccer players.
Neurotransmission-Related Polymorphisms			
ADRA2A	Various SNPs	Cardiorespiratory fitness	ADRA2A variants help modulate vascular tone and optimize oxygen distribution during physical activity

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ADRB2	Various SNPs	Bronchodilation, cardiovascular response	ADRB2 variants influence oxygen transport and utilization, enhancing endurance and stamina
BDNF	Val66Met	Neurogenesis, muscle regeneration	Val66Met (+) genotype influences brain microstructure and myelination in relation to soccer heading
DRD1	Various SNPs	Motivation, physical activity levels, dopamine regulation	DRD1 variants influence dopamine pathways, motivation, and physical activity levels, which are crucial for athletic performance
DBH	Various SNPs	Dopamine-to-norepinephrine conversion	DBH polymorphisms influence the conversion of dopamine to norepinephrine, impacting exercise performance and motivation.
Connective Tissue and Tendon-Related Polymorphisms			
COL1A1	-1997 G/T, +1245 G/T	Ligament injury risk	COL1A1 haplotypes linked to reduced risk of anterior cruciate ligament (ACL) rupture in professional soccer players.
COL2A1	Various SNPs	Cartilage structure, ligament injuries	No significant association with ACL rupture risk, though crucial for connective tissue integrity under mechanical stress.

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COL5A1	rs12722, rs13946	ACL injury risk	CC haplotype associated with lower ACL injury risk in soccer players.
ELN	Various SNPs	Medial collateral ligament (MCL) injury risk	ELN gene polymorphisms are linked to MCL injury rates, severity, and recovery time Certain ELN genotypes provide protection against MCL injuries
EMILIN1	Various SNPs	Elastin fiber integrity, tissue remodeling	EMILIN1 gene is involved in elastin fiber formation and tissue remodeling, potentially influencing injury risk and recovery in connective tissues
TNC	Various SNPs	Tendon structure, injury risk	TNC (Tenascin-C) gene regulates extracellular matrix remodeling and is linked to tendon injury risk and recovery times in athletes
Energy Metabolism-Related Polymorphisms			
AMPD1	34C/T	Energy metabolism, VO2 max	CT genotype associated with better response to creatine supplementation and reduced blood lactate accumulation.
MCT1	rs1049434	Lactate metabolism, injury risk	Players with AA genotype experience more injuries due to impaired lactate

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			transport and clearance.
UCP1, UCP2, UCP3, FTO	Various SNPs	Energy metabolism, muscle efficiency	Higher rates of energy uncoupling linked to improved muscle performance and ergometric efficiency.
Oxidative Stress and Detoxification-Related Polymorphisms			
GSTM1	Various SNPs	Oxidative stress response, detoxification	GSTM1 is involved in detoxification and the oxidative stress response, influencing recovery from the physical demands of soccer. Favorable variants may enhance recovery
GSTP	Various SNPs	Antioxidant defense, detoxification	GSTP contributes to the antioxidant defense system, helping to neutralize oxidative damage caused by intense physical activity, with implications for injury recovery
GSTT	Various SNPs	Oxidative stress, injury recovery	GSTT plays a key role in detoxification pathways, aiding recovery by reducing oxidative stress from high-intensity soccer matches and training sessions
Hormonal Regulation-Related Polymorphisms			
CYP2D6	Various SNPs	Drug metabolism, hormone regulation	Variations in CYP2D6 influence steroid hormone metabolism, potentially affecting endurance and recovery.

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HSD17B14	Various SNPs	Sprint performance, steroid metabolism	Influences muscle recovery and adaptation to high-intensity training.
Growth Factors and Muscle Hypertrophy-Related Polymorphisms			
GDF-8 (Myostatin)	Various SNPs	Muscle growth and strength	Myostatin variants influence muscle development and strength, important for soccer performance.
IGF2	Various SNPs	Muscle hypertrophy, injury risk	IGF2 polymorphisms linked to athlete status and increased muscle injury risk.
HGF	Various SNPs	Muscle regeneration, injury risk	HGF SNPs associated with injury severity and recovery times in soccer players.
PGC1a	Various SNPs	Mitochondrial biogenesis, energy metabolism	PGC1a (Peroxisome proliferator-activated receptor gamma coactivator 1-alpha) plays a crucial role in mitochondrial biogenesis and energy metabolism Variants are linked to enhanced endurance and professional athlete status in soccer players
Cell Signaling and Gene Expression-Related Polymorphisms			
GEFT			
NRF2	Various SNPs	Oxidative stress response, energy metabolism	NRF2 regulates oxidative stress response and energy metabolism, associated with playing position and

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			performance-related outcomes in soccer
PPARα	rs4253778	Fatty acid metabolism, energy homeostasis	PPARα is involved in fatty acid metabolism, with the G allele associated with professional athlete status and endurance in soccer players.
PPARGC1A	Various SNPs	Mitochondrial function, endurance performance	PPARGC1A is crucial for mitochondrial biogenesis and is linked to professional athlete status and endurance traits in soccer players.
PTPRK	Various SNPs	Cell signaling, muscle development	PTPRK (Protein tyrosine phosphatase receptor type K) influences muscle development and function, impacting soccer players' overall performance.
SOX15	Various SNPs	Muscle differentiation, gene regulation	SOX15 (SRY-box transcription factor 15) regulates muscle differentiation and is involved in the gene expression pathways crucial for athletic performance.
Inflammation and Immune Response-Related Polymorphisms			
CCL2	Various SNPs	Muscle inflammation, immune response	CCL2 gene involved in immune responses and muscle inflammation, impacting recovery and injury risk

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IL1RN	Various SNPs	Inflammatory response, injury recovery	IL1RN gene regulates inflammation, particularly in response to muscle damage, and is linked to improved recovery times and reduced injury risk.
IL6	Various SNPs	Inflammation, muscle repair	IL6 variants influence inflammation and muscle repair processes following intense physical activity. Increased IL6 levels are associated with muscle damage recovery.
LIF	Various SNPs	Muscle regeneration, injury recovery	LIF gene plays a role in muscle repair and regeneration following injury, influencing recovery times in soccer players.
Bone Health-Related Polymorphisms			
VDR	FokI, TaqI	Bone mass, muscle strength	VDR polymorphisms are associated with changes in bone mineral density and muscle strength in soccer players. Ff genotype linked to higher bone mass and IGF-1 levels.

3.2. Cardiovascular System-Related (ACE, AGT, NOS3, and VEGF) Polymorphisms in Soccer

ACE, the gene coding for the angiotensin-converting enzyme, a key enzyme involved in blood pressure regulation and fluid balance through the renin-angiotensin system (RAS) [17], has been found to correlate with athlete status and performance [18], both in male [19,20] and female [21] players, as well as with response to supplementation, including creatine intake [22]. More specifically, the polymorphic allele I was found to be associated with resistance and endurance increase, the allele D with strength and speed increase, and the heterozygous genotype with the power of the athlete [23,24]. According to a systematic review of the literature and meta-analysis [25],

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an increased prevalence of the ACE D allele was found among youth footballers (OR 1.18 [95%CI 1.01–1.38]), with the ACE DD genotype (OR 1.29 [95%CI 1.02–1.63]) exhibiting the strongest association. In the study by Micheli and colleagues [26], ACE-related polymorphisms were associated with the best performance in squat jump and countermovement jump. Furthermore, the ACE I/I genotype group was over-represented in the U17 category, with relatively older players exhibiting higher total genotype scores compared to their younger counterparts, particularly within the overall sample and among defenders [27]. In the study by Fatini et al. [28], the ACE genotype correlated with training-induced left ventricular mass change. In another study by Rizzo et al. [29], ACE polymorphism was linked to the degree of hypertrophy rather than the occurrence of left ventricular hypertrophy itself. The association of ACE-related genetic variants with cardiac morphology and functioning was replicated in the studies by Saber-Ayad et al. [30] and by Falahati and Arazi [31]. However, the studies by Falahati et al. [32,33] could not find any association with acute responses of cardiac biomarkers to intermittent and continuous exercise. Moreover, in the study by de Almeida et al. [34] soccer players with ACE II genotype were more susceptible to muscle injuries, possibly due to the impact of genetic factors on muscle recovery and performance. Conversely, while replicated in diverse ancestries, including Turkish and Japanese ones [35,36], ACE I/D polymorphisms were not associated with athlete status in Korean [37] and Brazilian [38] male footballers or with muscle power in Chinese elite and sub-elite youth male soccer players [39,40], potentially highlighting geographical/ethnic variations.

The angiotensinogen (AGT) gene plays a crucial role too in the RAS [41], contributing to the regulation of key physiological functions such as blood pressure, electrolyte balance, and vascular tone—all of which are essential for physical performance, particularly in sports like soccer that demand both endurance and explosive power. The AGT gene, particularly the rs699 polymorphism, has been studied for its potential influence on athletic performance. However, contrasting findings are reported in the literature. While a few studies could find associations with performance, cardiac, and hemodynamic parameters [42], these results have not been replicated among Brazilian soccer players [43].

The NOS3 gene codes for the nitric oxide synthase 3, which produces nitric oxide, influencing vascular tone and endurance performance [44–48]. The NOS3 -786 T/C polymorphism (rs2070744) has been identified as a potential genetic marker influencing individual variations in sports-related phenotypes. In a study [44] examining this polymorphism, the genotype and allele frequencies were determined in a cohort of 60 male elite soccer players and compared to those of 100 world-class endurance athletes, 53 elite power athletes, and 100 sedentary, healthy men (controls), all of Caucasian (Spanish) origin. Significant differences in genotype frequencies were observed between the soccer players and all other groups (controls, endurance athletes, and power athletes), with all comparisons yielding statistically significant results. Additionally, allele frequency analysis further confirmed these differences. These findings could be replicated in an Italian cohort [45]. Of note, the NOS3 Glu298Asp (rs1799983) polymorphism was associated with noncontact harmstring mscle injuy risk in a sample of 107 elite male outfield players prospectively followed for six seasons [46]. In another study [47], the NOS3 Glu/Glu allele was found to predispose players to the attacker and defender positions in elite soccer, as these roles are associated with greater strength and power metrics compared to midfielders.

Finally, the VEGF gene codes for the vascular endothelial growth factor, which stimulates blood vessel formation, linked to oxygen transport and endurance. As such, it plays a crucial role in athletic performance by promoting improved vascularization, which supports endurance by increasing capillary density and aiding adaptation to aerobic training. VEGF also accelerates muscle repair and recovery from injuries by promoting tissue regeneration. Additionally, the gene responds to low oxygen conditions, such as altitude training, enhancing performance by boosting oxygen-carrying capacity. The rs2010963 polymorphism has been found to enrich the genetic fingerprintings of professional athletes [49] and, along with other SNPs, it has been associated with performance outcomes after training interventions [50].

3.3. Muscle Structure and Function-Related (ACTN3, CKM, and MLCK) Polymorphisms in Soccer

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ACTN3, also known as the "speed gene", has been linked to sprinting and explosive power, as well as to performance metrics, even if to a varying extent [51]. Players with the RR genotype tend to have greater strength and speed, whereas those with the XX genotype (α-actinin-3 deficiency) may excel in endurance activities but are more susceptible to injuries. The study by Massidda and colleagues [52] examined the association between the ACTN3 R577X genotype and muscle injuries in 257 professional Italian football players compared to 265 nonathletic controls. Injury data was collected from a subgroup of 169 players over five seasons (2009-2014). Results showed that players with the ACTN3 XX genotype had 2.66 times higher odds of injury than those with the RR genotype, while RX and RR players had similar injury incidences. Additionally, XX players had 2.13 times higher odds of severe injuries than RR players, and RX individuals had 1.63 times higher odds of severe injuries than RR players. The research by Del Coso et al. [53] provides further compelling evidence that players with the ACTN3 XX genotype are more prone to muscle injuries and have reduced running performance. This study, involving over 300 elite soccer players in LaLiga, shows a strong correlation between genetic markers and both athletic performance and injury rates. On the other hand, in the study by Clos et al. [54], which reviewed non-contact musculoskeletal soft-tissue injuries in 43 professional football players across seven seasons (2007–2012 and 2015–2016), while a significant association was found between injury rate and the ACTN3 genotype, with the 577R allele present in 93% of the subjects, no statistically significant differences were observed in injury severity or recovery time linked to the ACTN3 SNP. Furthermore, the ACTN3 polymorphism can influence processes such as muscle recovery in professional soccer players. In a retrospective, observational study [55], DNA was extracted from blood samples to genotype ACTN3, and creatine kinase levels were measured 48 hours after matches. Sprint data, tracked using GPS, was collected from two cohorts of elite Brazilian soccer players. The main cohort consisted of 23 players from the top tier of the Brazilian Championship, and the replication cohort included 18 players from the First Division. In the main cohort, a significant positive correlation was found between the number of sprints and creatine kinase levels, particularly in players with the ACTN3 RR genotype, likely due to the presence of more type II muscle fibers, while no such relationship was observed in X allele carriers. Similar findings were observed in the replication cohort.

Finally, an interaction between ACE and ACTN3 polymorphisms has been found, which may help distinguish quantitative traits that are important for elite soccer performance. However, the overall contribution of genetic factors to soccer performance remains relatively modest [56].

The CKM gene, or muscle-specific creatine kinase gene, plays a vital role in energy metabolism within muscle tissue, particularly in skeletal muscles and the heart. The enzyme it encodes, muscle-specific creatine kinase, is essential for the phosphocreatine system, which facilitates the rapid regeneration of ATP during muscle contraction. This system becomes especially important during short bursts of high-intensity activities, such as sprinting or weightlifting, where immediate energy is crucial. Muscle-specifc creatine kinase converts creatine and ATP into phosphocreatine and ADP, providing an energy reserve that can be quickly accessed during muscle contractions. This process supports not only explosive muscle movements but also recovery, helping maintain ATP levels and reducing fatigue during intense exercise. Varillas-Delgado et al. [57] investigated the influence of the rs8111989 polymorphism in the CKM gene on injury incidence among 109 high-performance football players. Despite genotyping players into GG, GA, and AA groups, overall injury incidence did not differ significantly across these genotypes during training or match exposure. However, certain injury patterns were associated with specific genotypes. GG players experienced a higher frequency of slight-severity injuries and muscle contractures, while GA players were more prone to severe injuries and muscle tears. Additionally, G allele carriers had fewer gradual-onset and recurrent injuries compared to AA players, while A allele carriers had a higher frequency of severe injuries than GG players.

Finally, the MLCK gene codes for the myosin light chain kinase, which regulates muscle contraction. It has been found to be associated with athlete professional status [58], while the MYLK gene coding for the myosin light chain kinase and linked to muscle contraction and force generation has been found to be associated with muscle injuries in soccer players [59].

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3.4. Neurotransmission-Related (ADRA2A, ADRB2, BDNF, DRD1, and DBH) Polymorphisms in Soccer

The ADRA2A and ADRB2 genes, which are both associated with cardiorespiratory fitness, have been found to play a pivotal role in determining professional athlete status in a cohort of 292 professional athletes—160 elite endurance athletes and 132 professional football players— compared to 160 non-athlete individuals [58]. These genes regulate, indeed critical physiological functions such as heart rate, blood flow, and oxygen delivery during exercise. Variants in ADRA2A, encoding the alpha-2A adrenergic receptor, help modulate vascular tone and blood pressure, optimizing oxygen distribution during physical activity. Similarly, the ADRB2 gene, encoding the beta-2 adrenergic receptor, influences bronchodilation and cardiovascular response, allowing athletes to achieve superior oxygen transport and utilization. These genetic variants contribute to the enhanced endurance and stamina observed in elite athletes.

The BDNF gene codes for the brain-derived neurotrophic factor, which is linked to neurogenesis besides being associated with muscle repair, regeneration, and growth [60]. Hunter et al. [61] investigated whether the BDNF Val66Met polymorphism modifies the relationship between soccer heading and white matter microstructure in the brain. The study involved 312 amateur soccer players participating in the ongoing Einstein Soccer Study in New York City and surrounding areas. Researchers assessed the players' heading exposure over a 12-month period at the time of enrollment and two years later, using self-reported data. Diffusion tensor imaging was used to evaluate white matter microstructure, specifically focusing on radial diffusivity, a marker related to myelination in the brain. The study employed generalized estimating equations logistic regression models. A significant interaction was found between 12-month heading exposure and the BDNF Val66Met genotype on radial diffusivity. Players with the Met (+) genotype (those carrying the Met allele) exhibited significantly lower odds of having reduced radial diffusivity (indicating less myelination) when exposed to high levels of heading compared to those in the lowest quartile of heading exposure. The findings suggest that BDNF Val66Met (+) soccer players with high long-term heading exposure may have impaired re-myelination processes, which could explain the previously reported link between frequent heading and negative functional outcomes in soccer players.

Other genes related to neurotransmission that have been implicated in soccer science are the DRD1 gene and the DBH gene codes. The former codes for the dopamine receptor D1, which is involved in motivation, reward, and physical activity levels, while the latter codes for the dopamine beta-hydroxylase, which influences the conversion of dopamine to norepinephrine, linked to exercise performance and motivation [62].

Based on the observation that, as previously mentioned, elite professional soccer players have been found to display a preponderance of an allele associated with the NOS enzyme resulting in lower levels of nitric oxide compared to endurance athletes, power athletes, and sedentary men, Landers and Esch [48] suggested that this may reflect soccer's nature as an “externally-paced” sport, highly dependent on teamwork and executive function skills. One aspect of executive function is the skill of time interval estimation, which relies heavily on dopamine, a neurotransmitter involved in cognitive functions. Polymorphisms that affect dopamine pathways, such as the DRD2/ANKK1-Taq1a variant (which lowers D2 receptor density in the striatum, leading to increased dopamine synthesis), have been linked to both time interval estimation and executive skills. Genotypes among soccer players may influence cognitive abilities through neurotransmitter regulation, potentially predicting success in externally-paced sports like soccer. Interestingly, dopamine levels show an inverted-U relationship with both time interval estimation accuracy and executive skills, suggesting that optimal dopamine levels are crucial for these abilities. Research has also revealed a pathway from dopamine to the production of small quantities of NO through endogenous morphine and mu3 receptors on endothelial cells, with exercise up-regulating dopamine and this pathway. Excessive exercise can lead to negative feedback, where NO down-regulates dopamine to maintain optimal levels. In the context of professional soccer players, intense training, frequent public scrutiny, and stress can lead to elevated dopamine levels. However, without regulatory mechanisms, high dopamine could overwhelm the system. This is where the NOS3 -786T/C polymorphism, carried by many elite players, may play a protective role. The C allele of this variant leads to reduced NO

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production, preventing excessive negative feedback on dopamine and maintaining the balance necessary for peak cognitive and physical performance. These genetic adaptations may have evolutionary roots, with professional soccer players demonstrating a specialized mechanism for maintaining dopamine levels under intense physical and cognitive demands.

3.5. Connective Tissue and Tendon-Related (COL1A1, COL2A1, COL5A1, ELN, EMILIN1, and TNC) Polymorphisms in Soccer

COL1A1 is a gene that encodes for the alpha-1 chain of type I collagen, which is the most abundant collagen in the human body. Type I collagen is a major structural protein found in skin, bone, tendons, ligaments, and other connective tissues, providing strength and support. Ficek and colleagues [63] aimed to explore the relationship between the COL1A1 -1997G/T and +1245G/T gene polymorphisms, individually and as haplotypes, and the occurrence of anterior cruciate ligament ruptures in professional soccer players. The research involved 91 male professional soccer players who had undergone surgery for a primary anterior cruciate ligament rupture, compared to a control group of 143 healthy male soccer players with no reported history of ligament or tendon injuries. All participants were of Polish or East-European descent (for at least three generations), belonged to the same teams, were of a similar age, and had comparable exposure to anterior cruciate ligament injury risk. A higher frequency of the COL1A1 G-T haplotype was significantly linked to a reduced risk of anterior cruciate ligament rupture. The TT genotype was less common in the anterior cruciate ligament rupture group, but this was not statistically significant. In conclusions, the COL1A1 G-T haplotype is associated with a lower risk of anterior cruciate ligament injury in professional soccer players, suggesting that carrying two copies of this haplotype may provide protection against anterior cruciate ligament ruptures.

The COL2A1 gene encodes the alpha-1 chain of type II collagen, which is a crucial component of cartilage, the intervertebral discs, and the vitreous humor of the eye. Type II collagen is a fibrillar collagen primarily found in cartilage and is essential for maintaining the structural integrity and proper function of connective tissues, particularly those that are subjected to mechanical stress. Sun et al. [64] tested the hypothesis that two specific SNPs, rs11784270 (A/C) and rs6577958 (C/T), within the COL22A1 gene are associated with anterior cruciate ligament ruptures in Polish soccer players. A total of 228 athletes with anterior cruciate ligament injuries (157 men and 71 women) and 202 control athletes (117 men and 85 women) participated in the study. The results showed no significant association between the SNPs and the risk of non-contact anterior cruciate ligament ruptures.

The COL5A1 gene, which encodes the collagen alpha-1(V) chain, plays a key role in supporting tissues rich in type I collagen, including muscles, tendons, and ligaments. It is involved in regulating the structure of fibers composed of both type I and type V collagen. Given this role, the study by Lulińska-Kuklik [65] investigated the association between the COL5A1 rs12722 and rs13946 polymorphisms, both individually and as haplotypes, and the risk of anterior cruciate ligament rupture in professional soccer players. The study included 134 male soccer players with surgically confirmed anterior cruciate ligament ruptures and 211 healthy male players without any reported ligament or tendon injuries. Both groups were recruited from the same teams, were of similar ages, and had comparable exposure to anterior cruciate ligament injury risk. The results showed statistically significant differences in the genotype frequencies for the rs13946 polymorphism in a dominant inheritance model. Additionally, the CC haplotype of rs12722 and rs13946 was significantly less represented in the anterior cruciate ligament rupture group compared to the controls, suggesting a protective effect against anterior cruciate ligament injury. From a gender perspective, Rodas et al. [66] explored the sex-specific risk of non-contact anterior cruciate ligament rupture in relation to SNPs in collagen genes among elite football players. The research included 46 FC Barcelona footballers (24 females) from the 2020-21 season, examining the association between 108 selected SNPs and a history of non-contact anterior cruciate ligament injuries, stratified by sex. Results showed that 29% of female players and 4% of male players had experienced non-contact anterior cruciate ligament ruptures. A significant association was found between the rs13946 CC genotype and anterior cruciate ligament injury in female players, with no significant findings in

 doi:10.20944/preprints202410.1705.v1

males. The interaction between the rs13946 SNP and sex was also significant, with the C-allele being exclusive to a specific haplotype in the COL5A1 gene. The authors concluded that SNPs in collagen-encoding genes may increase the risk of anterior cruciate ligament injuries in female footballers, highlighting the potential for genetic profiling to inform sex-specific injury prevention strategies.

Artells et al. [67] explored the relationship between SNPs in the elastin (ELN) gene and medial collateral ligament injuries in football players. Sixty elite football players were analyzed for SNPs in the ELN gene using Allelic Discrimination analysis and monitored for medial collateral ligament injuries over seven seasons. The findings showed that specific ELN genotypes were linked to medial collateral ligament injury rates, severity, and recovery time. Players with the ELN AA genotype experienced 16 medial collateral ligament injuries, while those with the ELN AG genotype had 3. Notably, players with the ELN GG genotype sustained no medial collateral ligament injuries. The study concluded that identifying ELN gene polymorphisms could help predict injury risk, guide training and rehabilitation plans, and optimize recovery and workload management to prevent MCL injuries.

3.6. Energy Metabolism-Related (AMPD1, FTO, MCT1, UCP1, UCP2, and UCP3) Polymorphisms in Soccer

The AMPD1 gene codes for the adenosine monophosphate deaminase 1, which plays a role in energy metabolism during exercise [20,68]. Lifanov et al. [69] assessed the impact of short-term creatine supplementation on exercise performance in male athletes, considering their genetic makeup. Athletes demonstrated a significantly higher frequency of the T allele in AMPD1 34T compared to controls. During the experimental phase, 21 football players were randomly assigned to either the creatine group (n=11) or the placebo (dextrose) group (n=10). The AMPD1 CC genotype showed the best response to creatine supplementation. Notably, the increase in relative VO_{2max} was significantly greater in AMPD1 CT genotype carriers compared to AMPD1 CC genotype carriers. Additionally, there was a reduced blood lactate accumulation in AMPD1 CT genotype carriers compared to AMPD1 CC genotype carriers.

The MCT1 gene codes for the monocarboxylate transporter-1, which plays a crucial role in regulating lactate metabolism that is particularly important in muscle function and recovery. MCT1 is responsible for the transport of lactate and other monocarboxylates (such as pyruvate) across cell membranes, including muscle cells. The proper transport and clearance of lactate are essential for maintaining muscle pH and preventing acidosis, which can lead to muscle fatigue and injury. A study was conducted by Massidda and coauthors [70] on 173 elite male Italian football players to examine the association between the MCT1 rs1049434 polymorphism and the incidence of indirect muscle injuries. The players, recruited from various levels of a first-league football club, were genotyped for the MCT1 polymorphism, and muscle injury data were collected over five football seasons (2009-2014). Indirect muscle injuries included structural-mechanical injuries and functional muscle disorders. The results indicated that players with the MCT1 AA genotype experienced significantly more injuries compared to those with the TT genotype. The study concluded that the MCT1 rs1049434 polymorphism is linked to a higher incidence of muscle injuries, even though the statistical significance was nominal.

The UCP1, UCP2, and UCP3 genes, which code for the uncoupling proteins 1, 2, and 3, are involved in energy regulation and metabolism. Bondareva et al. [71] investigated the polymorphisms of uncoupling protein genes in football players, comparing the results to those of non-athletes. A higher percentage of carriers of the “energy-sparing” allele in the UCP3 gene could be observed. A similar trend was observed in the allele frequencies of the other genes studied. This finding may be partially explained by the need for energy conservation in athletes' bodies. Spearman rank correlation analysis revealed a significant association between the UCP1 gene and the elastic component of explosive leg muscle strength. No significant correlations were found with overall body composition or fat distribution, except for fat distribution in the pelvic area. The UCP2 gene was correlated with respiratory function parameters, while UCP3 was linked to the rate of energy production during ramp testing and ergometric efficiency parameters. Additionally, a higher rate of uncoupling

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between oxidation and phosphorylation in muscles was found, leading to an increase in total energy consumption, while also enhancing ergometric efficiency and muscle performance near the anaerobic threshold.

Similar trends could be reported for the FTO (Fat Mass and Obesity-associated) gene, primarily known for its role in regulating body weight and energy homeostasis. This gene encodes a protein that functions as a DNA/RNA demethylase, influencing the metabolism of fat and, consequently, body composition [71].

3.7. Oxidative Stress and Detoxification-Related (GSTM1, GSTP, and GSTT) Polymorphisms in Soccer

The GSTM1 gene coding for the glutathione S-transferase Mu 1, an enzyme involved in oxidative stress response and detoxification, the GSTP gene encoding the glutathione S-transferase pi, part of the antioxidant defense system, and the GSTT gene coding for the glutathione S-transferase theta, another key enzyme in oxidative stress and detoxification pathways, have been linked to professonal athlete status in football players [58]. These SNPs indeed may influence the athletes' capacity to cope with oxidative stress and recover from the high-intensity physical demands of the sport. Athletes with favorable variants of these genes may have enhanced resistance to oxidative damage and improved detoxification efficiency, potentially giving them an advantage in terms of recovery, endurance, and performance.

3.8. Hormonal Regulation-Related (CYP2D6 and HSD17B14) Polymorphisms in Soccer

The CYP2D6 gene codes for the cytochrome P450 2D6, part of the larger cytochrome P450 family, which is involved in drug metabolism, and steroid hormone and neurotransmitter regulation. CYP2D6 is responsible for the metabolism of about 20-25% of commonly prescribed drugs, influencing how individuals process medications, making it important for personalized medicine. Variations in the CYP2D6 gene can lead to different metabolizer types: namely, poor, intermediate, extensive, or ultra-rapid metabolizers, which can significantly affect an individual's response to medication or other exogenous compounds [72]. It has been linked to professonal athlete status in football players [58]. It can be speculated that the enzyme’s role in hormone regulation may influence physical endurance, recovery, and the body's ability to adapt to strenuous physical activity. Hormonal balance, including the regulation of cortisol and other stress-related hormones, could play a part in maintaining optimal performance under intense physical and psychological stress. Moreover, genetic variations in CYP2D6 might influence an athlete's susceptibility to injury or their ability to metabolize substances such as painkillers or anti-inflammatory drugs, which are commonly used in professional sports settings.

The HSD17B14 gene codes for the hydroxysteroid 17-beta dehydrogenase 14, which is involved in steroid hormone metabolism. It has been associated with sprint test performance in elite youth football players [42]. Sprinting, which demands explosive muscle power and rapid energy mobilization, is, indeed, influenced by the balance of anabolic and catabolic hormones. The ability to rapidly metabolize steroid hormones may give certain athletes a genetic advantage in terms of muscle recovery, energy efficiency, and adaptation to high-intensity training, all of which are critical factors in sprinting performance.

Overall, these genetic factors may help explain why some football players excel in short, intense bursts of activity such as sprints, which are crucial in football for chasing the ball, overtaking opponents, or breaking into open spaces.

3.9. Growth Factors and Muscle Hypertrophy-Related (GDF-8, IGF2, HGF, and PGC1a) Polymorphisms in Soccer

Myostatin (GDF-8), a member of the TGF-β (transforming growth factor-beta) family, is a key regulator of muscle growth, and its role in sports performance has attracted attention, particularly in soccer. Polymorphisms or genetic variations in the MSTN gene, which encodes GDF-8, can affect

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muscle development, strength, and endurance, traits crucial for athletic performance. Specific SNPs such as K153R, E164K, P198A, and I225T have been identified in the GDF-8 gene [20].

The gene IGF2 encodes the insulin-like growth factor 2, involved in muscle hypertrophy and growth. SNPs in these gene have been linked to professional athlete status and increased injury risk [42,73,74].

The gene HGF codes for the hepatocyte growth factor, which is important in muscle regeneration and repair. Liver metabolism plays, indeed, a crucial role in muscle health by regulating energy production, detoxification, protein synthesis, and fat metabolism. Disruptions in liver function can lead to energy deficits, slower muscle recovery, inflammation, and hormonal imbalances, all of which increase the risk of muscle injuries in footballers. Pruna et al. [73] investigated the role of SNPs in the HGF gene to understand interindividual differences in injury severity, recovery time, and injury rate in elite soccer players. The aim was to identify genetic biomarkers that could help prevent or minimize non-contact muscle injuries. Genomic DNA from 74 elite soccer players was analyzed using allelic discrimination techniques. The results showed that SNPs in the HGF gene were significantly associated with injury incidence, severity, and recovery time.

Finally, the gene PGC1a coding for the peroxisome proliferator-activated receptor gamma coactivator 1-alpha, and regulating energy metabolism and mitochondrial biogenesis, has been associated with professional athlete status in footballers [58].

3.10. Cell Signaling and Gene Expression-Related (GEFT, NRF2, PPARA, PPARGC1A, PTPRK, and S0X15) Polymorphisms in Soccer

The NRF2 gene encoding the nuclear factor erythroid 2-related factor 2 which regulates oxidative stress response and energy metabolism has been associated with playing position and performance-related outcomes [75].

The PPARα gene, which codes for the peroxisome proliferator-activated receptor alpha and regulates genes involved in fatty acid metabolism and energy homeostasis, was studied by Proia et al. [76] to determine the prevalence of the G allele of the PPARα intron 7 G/C polymorphism (rs4253778) in professional Italian soccer players. The study involved 60 professional soccer players and 30 sedentary volunteers. The results showed that the G allele and GG genotype were significantly more common in soccer players than in sedentary controls. However, no significant correlations were found between lipid profiles and genotype. The findings suggest that the G allele and GG genotype, previously linked to endurance athletes, are also prevalent in professional soccer players.

The PPARGC1A gene, coding for the peroxisome proliferator-activated receptor gamma coactivator 1-alpha, which regulates mitochondrial biogenesis and energy metabolism, has been linked to athlete status and performance-related outcomes [77], as well as PTPRK (protein tyrosine phosphatase receptor type K), SOX15 (SRY-box transcription factor 15), GEFT (guanine nucleotide exchange factor T).

3.11. Inflammation and Immune Response-Related (CCL2, IL1RN, IL6, and LIF) Polymorphisms in Soccer

Several genetic variants related to inflammation and immune responses have been linked to performance outcomes and injury risk in footballers [73,74,78]. These include the CCL2 gene coding for the C-C motif chemokine ligand 2, which is involved in the immune response and muscle inflammation, the IL1RN gene coding for the interleukin 1 receptor antagonist, which regulates inflammation, particularly in response to muscle damage, the IL6 gene encoding the interleukin 6, which is involved in inflammation and muscle repair following exercise, and the LIF gene coding for the leukemia inhibitory factor, which plays a role in muscle repair and regeneration after injury.

3.12. Bone Health-Related (VDR) Polymorphisms in Soccer

The vitamin D receptor (VDR) gene influences several musculoskeletal traits, with polymorphisms in this gene previously linked to various pathologies and muscle strength in athletes. Diogenes et al. [79] investigated the role of common VDR variants (FokI and TaqI) on longitudinal

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changes in bone mass and calcium-related hormones among 46 adolescent soccer players, aged 11.8 to 14.2 years. Total body bone mineral content (TBMC) and density (TBMD) were assessed at baseline and after 6 months, while levels of insulin-like growth factor-I (IGF-1), testosterone, intact parathyroid hormone, and plasma bone alkaline phosphatase activity were measured at baseline and after 3 months. At baseline, boys with the Ff genotype exhibited significantly higher TBMC, TBMD, and TBMD Z-scores compared to those with the FF genotype. Additionally, after 3 months, the Ff genotype group showed a significantly greater increase in plasma IGF-1 levels. Although the FokI polymorphism did not influence changes in bone mass after 6 months, the differences observed at baseline persisted. No significant differences were found in bone mass, hormone levels, or other outcome variables based on TaqI genotypes. Flore et al. [80] investigated the relationship between the most commonly studied VDR gene variants (rs2228570, rs7975232, and rs1544410) and muscle mass gains in elite young soccer players. A cohort of 55 soccer players aged 15-18 from a professional team was selected for this research. All three polymorphisms were found to be in Hardy-Weinberg equilibrium, with allele frequencies consistent with global population variability. A significant association was identified between the rs1544410 polymorphism and increased calf muscle mass. Specifically, individuals carrying the A allele had greater calf muscle mass compared to those with the G allele. Furthermore, haplotype analysis of the two SNPs in linkage disequilibrium (rs7975232 and rs1544410) revealed that the AG haplotype was negatively correlated with calf muscle area.

3.13. Shifting from Single Nucleotide Polymorphisms to Polygenic Approaches

Shifting from SNPs to polygenic approaches, as a recent trend in soccer, reflects a move toward a more holistic understanding of genetic contributions to athletic performance. While SNPs focus on individual genetic variations, polygenic approaches aggregate multiple variants to provide a broader, more accurate prediction of traits like endurance, speed, and injury risk, enabling personalized training and talent identification.

Petr et al. [47] examined the influence of several specific genetic variants on performance in speed, power, and strength laboratory tests among elite soccer players, including their playing positions. Ninety-nine male elite soccer players were compared to 107 controls and underwent isokinetic strength testing of the quadriceps and hamstrings at different speeds (60°/s, 180°/s, and 300°/s), along with jump performance. The genotypes studied included ACTN3 (R577X, rs1815739), ACE (I/D, rs1799752), NOS3 (Glu298Asp, rs1799983), AMPD1 (34C/T, rs17602729), UCP2 (Ala55Val, rs660339), BDKRB2 (+9/-9, rs5810761), and IL1RN (VNTR 86-bp). The study found that defenders with the ACTN3 XX homozygous genotype had lower quadriceps and hamstring strength across all tested speeds compared to ACTN3 RX and RR genotypes. Additionally, ACTN3 RR homozygotes among defenders exhibited higher quadriceps strength at all tested velocities than RX heterozygotes. Other associations were observed between playing positions and genetic predispositions: AMPD1 CC, NOS3 Glu/Glu genotypes, and IL1RN*2 allele carriers were linked to increased lower limb strength, particularly in attackers and defenders. Total genetic score regression explained 26% of the variance in jump performance and isokinetic strength. The findings suggest that the ACTN3 R allele, NOS3 Glu/Glu genotype, and IL1RN*2 allele predisposed certain players, particularly attackers and defenders, to higher strength and power measures. In contrast, midfielders showed lower strength and power, which appeared unrelated to the strength and power genes studied.

Egorova et al. [81] investigated the association of common gene polymorphisms with football player status, individually and in combination. A total of 246 Russian football players and 872 controls were genotyped for eight gene polymorphisms known to be associated with athletic status. Four specific alleles (ACE D, ACTN3 Arg577, PPARA rs4253778 C, and UCP2 55Val) were identified as having discrete associations with football player status. Football players had a significantly higher mean total genotype score compared to controls, indicating that individuals with a higher number of "favorable" gene variants have an increased likelihood of becoming football players.

Contrò et al. [75] developed an innovative genetic framework to evaluate the likelihood that soccer players possess a favorable genetic background that enhances performance by analyzing specific Performance Enhancing Polymorphisms (PEPs) in five genes: PPARα, PPARGC1A, NRF2,

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ACE, and CKMM. The study focused on understanding how each polymorphism, individually or through interaction with others, contributes to distinguishing elite athletes from the general population. Sixty professional soccer players and sixty healthy non-athletes participated. The results showed a statistically significant association between the NRF2 (AG/GG genotype) polymorphism and soccer players, with an even stronger association found for the ACE polymorphism. Notably, the ACE ID genotype and, even more so, the II genotype were closely linked to the soccer player phenotype. While the other PEPs did not show direct statistical significance, the study indicated that some may have indirect effects by enhancing the influence of other polymorphisms. For example, PPARα appeared to amplify the effect of the NRF2 (GG) polymorphism, despite not showing significance on its own.

To account for these interplays of effects [82], Maestro et al. [83] calculated a total genotype score to quantify the combined influence of six polymorphisms (AMPD1, ACE, ACTN3, CKM, and two MLCK variants) on injury risk. A total of 122 male professional football players were recruited and analyzed for these polymorphisms using Single Nucleotide Primer Extension (SNPE). A score of 2 was assigned to "protective" genotypes, 1 to heterozygous genotypes, and 0 to the "worst" genotypes for injuries. Key findings included significant differences in the distribution of allelic frequencies of AMPD1 and MLCK polymorphisms between non-injured and injured players. The average total genotype score for non-injured players was higher than for injured players.

This approach has ben leveraged also by Massidda et al. [84], who recruited sixty-four male top-level football players. These were genotyped for four specific gene polymorphisms: ACE I/D (rs4341), ACTN3 c.1729C > T (rs1815739), COL5A1 C > T (rs2722), and MCT1 c.1470A > T (rs1049434). Muscle injuries over a ten-year period were analyzed, with the results indicating that the distribution of certain polymorphisms (ACE I/D, ACTN3, MCT1) differed significantly between injured and non-injured players. A higher presence of "protective" gene variants correlated with a lower incidence of muscle injuries. Non-injured players had a higher total genotype score compared to injured players.

Similarly, McAuley et al. [85] explored the relationship between 22 SNPs and key athletic traits such as acceleration, change of direction, jump height, and speed in 149 male academy football players, aged under-12 to under-23, from four English academies. The players performed various sprints, countermovement jumps, and agility tests. Simple linear regression was used to analyze individual SNP associations, while total genotype scores were calculated to assess the combined impact of all SNPs. Notably, the GALNT13 (rs10196189) G allele was linked to faster sprint times (~4% improvement), and the IL6 (rs1800795) G/G genotype was associated with higher countermovement jumps performance (~16% improvement). Overall, the combined genetic scores significantly correlated with all performance metrics, accounting for 6 to 33% of the variance.

While a few studies using the total genotype score have been published [86], there is currently a single genome-wide association study (GWAS) [42], which was conducted to identify genetic variants linked to sprint performance in elite youth football players. Using microarray data, the researchers analyzed 1,206 subjects, identifying 12 SNPs with suggestive significance after replication. The study also validated some of the discovered SNPs in additional cohorts.

3.14. Current Limitations of Genomics in Soccer Research and Future Directions

Genomic testing offers a powerful means to tailor training programs to an athlete's genetic predispositions, optimizing performance while reducing injury risks, as PEPs are subject to selective pressures [87]. However, current research in soccer often lacks sufficient ethnic diversity and fails to provide a detailed analysis of players' field positions. Additionally, the role of psychological traits in football performance remains underexplored. To address these gaps, future studies should adopt more robust research designs, increase sample sizes, and integrate advanced genetic methodologies such as GWAS and polygenic profiling.

In response to these limitations, the Football Gene Project was recently introduced. This initiative seeks to foster individualized athlete development by incorporating genetic, psychological, and positional factors into training protocols [15,16]. A deeper understanding of how polymorphisms influence athletic performance requires examining the complex interactions between genetic

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variations, which may be crucial to unlocking an individual's full genetic potential for elite performance.

Traditional genetic and genomic association studies in soccer players are often hampered by inconsistent findings across populations, influenced by diverse genetic backgrounds, environmental factors, and specific physiological traits. These inconsistencies highlight the need for replication, validation, and confirmation before genetic findings can be reliably applied to sports science. For instance, Kanope et al. [87] conducted a groundbreaking study by fully sequencing the genomes of 44 male Brazilian first-division under-20 soccer players (U20_BFDSC) and comparing them to global population databases (1000 Genomes). Their research aimed to provide an alternative to traditional genetic association studies through genetic distance matrix and molecular variance analyses. Surprisingly, the U20_BFDSC players exhibited significantly higher genetic differentiation from African populations, despite previous studies suggesting a genetic similarity between Brazilian and African populations (12-24%). The U20_BFDSC players were more genetically similar to professional athletes, suggesting that intense genetic selection pressures related to performance might occur before full maturation.

This study and a similar one [88] show that performance-related genes are likely influenced by a combination of physical, environmental, cognitive, and sociocultural factors. Cutting-edge molecular variance analysis and Wright's statistics can offer valuable insights into performance-related genetic differences in soccer science.

3.15. Proteomics in Soccer

Proteomics, the study of the entire set of proteins expressed in a cell or organism, is particularly useful for understanding muscle physiology and recovery. Proteins are central to muscle repair and inflammation, and analyzing their expression can provide insights into how well an athlete is recovering from strenuous exercise or injury [89–91].

Currently, there exist only a few studies applying proteomics in scoccer science. Martín-Sánchez et al. [90] aimed to investigate whether an intensive pre-season training program affects the inflammatory status of professional soccer players and how this may be linked to their physical condition. The researchers compared plasma protein biomarkers, cardiac function, and physiological state between 12 professional and 9 recreational soccer players. Following the training, professional players exhibited reduced cardiac low frequency compared to recreational players, though no significant differences were observed in other cardiac measures (e.g., high frequency, oxygen consumption). Proteomic analysis revealed that certain inflammatory and oxidative stress-related proteins, such as alpha-1-antitrypsin isotype-3 and fibrinogen-gamma, were reduced in professional players, while others like alpha-1-antitrypsin isotype-6 and alpha-1-antichymotrypsin increased. Spearman's correlation showed a positive association between cardiac low frequency and fibrinogen-gamma isotype 3, and a negative correlation between cardiac low frequency and alpha-1-antichymotrypsin isotype 4. These findings suggest that intensive pre-season training in professional soccer players influences plasma proteins related to inflammation, oxidative stress, and thrombosis.

4. Current Limitations of Proteomics in Soccer Research and Future Directions

Despite its potential, proteomics in soccer science faces several limitations. One major challenge is the complexity of protein expression, which can vary greatly depending on factors like training load, injury status, diet, and individual physiology. The high cost and technical expertise required for proteomic analysis limit its widespread use in soccer research. Moreover, standardizing sample collection, processing, and analysis is difficult due to the variability in protein expression across different biological matrices (e.g., blood, muscle tissue, or urine). This variability makes it challenging to draw definitive conclusions and apply findings universally. Future directions should focus on expanding the sample sizes in studies, integrating proteomics with other “omics” approaches (like metabolomics and genomics) to gain a more holistic view of an athlete's health and recovery, and developing cost-effective, accessible technologies for routine monitoring in sports settings.

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Collaborations between sports scientists, bioinformaticians, and clinicians will be key to translating proteomics research into practical applications for enhancing performance and recovery in soccer.

4.1. Metabolomics in Soccer

Metabolomics, which involves the study of small molecules (metabolites) within cells, tissues, or organisms, offers valuable insights into energy metabolism and recovery processes in athletes. The ability to track metabolite fluctuations provides real-time feedback on an athlete's physiological state, which can be used to adjust training intensity or nutritional interventions [92].

Książek et al. [93] investigated novel markers of vitamin D status, including free 25-(OH)D, bioavailable 25-(OH)D, and the vitamin D metabolite ratio (VMR), alongside psychophysical stress markers during different training periods over half a season in professional football players. Twenty athletes were tested at six time points over six months to assess seasonal variations in vitamin D binding protein (VDBP), total and free 25-(OH)D, and other vitamin D metabolites. Results showed a significant seasonal rhythm in VDBP, total and bioavailable 25-(OH)D, and various vitamin D metabolites, but no rhythm was observed for free 25-(OH)D or psychophysical stress markers (ferritin, liver enzymes, CK, testosterone, cortisol, and testosterone-to-cortisol ratio). Despite the seasonal variations in some vitamin D markers, no correlation was found between vitamin D measurements and psychophysical stress markers. The study also found a strong correlation between 25-(OH)D3 and 24,25-(OH)2D3 during all training periods, but training loads did not influence resting vitamin D metabolite concentrations. Ultimately, free 25-(OH)D did not prove superior to total 25-(OH)D in reflecting vitamin D status in relation to stress markers.

Ra and colleagues [94] used metabolomics to identify salivary fatigue markers in soccer players after three consecutive days of games. The study involved 122 male soccer players, and traditional fatigue symptoms such as heart rate, body mass, and mood were measured before and after the program. Out of the participants, 37 players showed signs of fatigue. Saliva samples from these fatigued players were analyzed using capillary electrophoresis and time-of-flight mass spectrometry, with data processed using principal component analysis. Metabolomics identified 144 metabolites in the saliva of fatigued players, showing significant metabolic changes before and after the three-day game program. All metabolites were increased post-program, with notable metabolites like 3-methylhistidine, glucose 1- and 6-phosphate, taurine, and several amino acids involved in muscle breakdown, glucose metabolism, lipid metabolism, amino acid metabolism, and energy metabolism.

Another example of metabolomics in soccer is the study by Gouveia et al. [95], which used metabolomic profiling to monitor changes in the urinary metabolites of elite female soccer players throughout a championship season. The study identified several metabolites linked to energy and protein metabolism, including glycine, citrate, and urea, that showed significant variation pre- and post-match.

Kim et al. [96] analyzed urinary metabolites in young Korean soccer players after 1, 5, and 10 days of winter training seeason using nuclear magnetic resonance spectroscopy and multivariate analysis to recommend optimal recovery times for improving performance. A total of 79 metabolites were identified from urine samples, with 15 metabolites—such as 1-methylnicotinamide, 3-indoxylsulfate, galactarate, glutamate, and lactate—showing significant changes after winter training seeason. These metabolites are involved in key metabolic processes, including the urea, purine nucleotide, and glucose-alanine cycles. Most metabolites spiked after 1 day of winter training season and returned to normal levels. However, four metabolites—adenine, 2-hydroxybutyrate, alanine, and lactate—remained elevated for 5 days post-training, suggesting that at least 5 days of recovery are needed based on excess ammonia, adenine, and lactate levels.

Similarly, Pintus et al. [97] conducted a ^{1}H-NMR analysis of urine samples from 21 professional soccer players at three different points during the preseason preparation for the Serie A Championship in Italy. The study revealed that the urinary metabolite profile changed over the observational period. Notably, significant variations were observed in the levels of trimethylamine-N-oxide, dimethylamine, hippuric acid, hypoxanthine, guanidoacetic acid, 3-hydroxybutyric acid, citric acid, and creatine. These changes were likely influenced by factors such as diet, training

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regimen, and gut microbiota. For example, trimethylamine-N-oxide and hippuric acid, both of dietary origin, are also linked to microbiota activity, while 3-hydroxybutyric acid is associated with the type of physical exercise.

França et al. [98] investigated the impact of soccer exercise on tyrosine metabolism using an untargeted, sportomics-based analysis of urine samples from 30 male junior professional soccer players. Samples were collected before and after a match and analyzed via liquid chromatography and mass spectrometry. The results showed significant changes in tyrosine metabolism, including a downregulation of homogentisate metabolites (4-maleylacetoacetate and succinylacetone) by 80% and 84%, respectively, and an upregulation of 4-hydroxyphenylpyruvate by 26%. Hawkinsin and its metabolite 4-hydroxycyclohexyl acetate increased six-fold, while DOPA and dopaquinone levels rose four- to six-fold. Conversely, 3-methoxytyrosine, indole-5,6-quinone, melanin, dopamine, and tyramine decreased by up to 99%. Blood TCO_2 and urinary glutathione and glutamate decreased, with a two-fold increase in pyroglutamate. The metabolic changes observed bore unexpected similarities to Hawkinsinuria, suggesting a transient condition termed exercise-induced hawkinsinuria, indicating that soccer exercise could serve as a model to explore potential treatments for Hawkinsinuria and other disorders affecting tyrosine metabolism.

Finally, Peña et al. [99] leveraged lipidomics to explore the lipid profile of mature erythrocyte membranes in professional female football players to assess their metabolic and nutritional status during the football season. It aimed to compare their lipid profile with optimal values for the general population and a control group. The observational study involved female football players from Athletic Club Bilbao, with blood samples collected at three time points over three consecutive seasons (2019-2022), resulting in 160 samples from 40 women. The lipid profile of mature erythrocyte membranes analysis revealed significant increases in docosahexaenoic acid (DHA) and total polyunsaturated fatty acids (PUFA) during the first season, and a buildup of arachidonic acid (AA) and PUFA during the second season with intense training. Compared to the general population, the players showed lower levels of omega-6 dihomo-γ-linolenic acid (DGLA) and elevated levels of AA, eicosapentaenoic acid (EPA), and the ratio of saturated and monounsaturated fatty acids (SFA/MUFA). Mild negative correlations were found between certain fatty acids and vitamin D, urea, cortisol, and age. The study concludes that significant variations in membrane fatty acids occur during the competitive season, especially an increase in PUFAs and a decrease in DGLA, which is involved in immune and anti-inflammatory responses.

4.2. Current Limitations of Metabolomics and Lipidomics in Soccer Research and Future Directions

Overall, these findings suggest that metabolomic data can be instrumental in understanding fatigue, energy expenditure, and recovery needs, while lipidomics could be a valuable tool for developing personalized nutritional strategies for elite football players to address metabolic imbalances during the season. On the other hand, metabolomics studies present some challenges, particularly in the analysis of saliva samples from athletes. One major issue is the variability in data normalization methods, such as whether to use total protein or total metabolite concentrations, which can significantly affect the interpretation of results. Additionally, saliva as a biofluid poses its own limitations—systemic responses to exercise are short-lived in saliva compared to blood, making it difficult to capture lasting metabolic changes. The heterogeneous nature of soccer players' activities during a match and the timing of sample collection further complicate the ability to draw consistent conclusions about metabolic shifts. These challenges are compounded by the fluctuating water content in saliva, which demands precise normalization to accurately reflect metabolic changes. The variation in physical exertion among players also affects the consistency of measurable metabolic markers. Despite these obstacles, overall findings suggest that metabolomic data can be instrumental in understanding fatigue, energy expenditure, and recovery needs in athletes, provided that the methodological complexities are carefully managed [92,100,101].

4.3. Microbiomics in Soccer

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The gut microbiome, composed of trillions of microorganisms residing in the digestive tract, plays a critical role in maintaining overall health, immune function, and even athletic performance. Research has increasingly shown that athletes with a healthier, more diverse gut microbiota recover faster and perform better over time [102,103].

However, there exist a few studies that report gut microbiota parameters in elite soccer players and provide insights into how varying physical activity levels affect gut microbiota composition. Petri et al. [103] investigated the relationship between physical activity levels and gut microbiota composition by comparing four groups of healthy young males: 17 elite soccer players, 14 individuals with high physical training, 23 with moderate physical activity, and 37 sedentary men. Key findings included a significantly higher prevalence of nine microbiota populations in elite soccer players and highly active individuals compared to those with moderate or no physical activity. However, there were no differences in the Firmicutes to Bacteroidetes ratio among the groups.

Urban et al. [104] analzyed 20 professional football players and 12 amateurs. The results showed that oral microbiota diversity was similar between both groups, though increased training intensity led to a reduction in bacterial species. However, the gut microbiota revealed a significant difference between professionals and amateurs, especially during intensive training. Firmicutes dominated the microbial population across all groups. Intensive physical activity was associated with an increase in butyrate- and succinate-producing bacteria, which are beneficial for maintaining metabolic homeostasis and supporting immune system function, underscoring the positive impact of exercise on gut microbiota and overall health.

Kenger et al. [105] investigated the relationship between microbiota profiles and the nutritional status of professional football players who perform endurance exercises. Twenty male professional footballers from a Turkish Football Federation Second League club participated in the study. Fecal samples were collected and analyzed through 16s rRNA gene sequencing, and the players' body composition was measured using a bioelectrical impedance analyzer. The participants' 3-day food intake was recorded with the assistance of a dietitian. The analysis identified four phyla, 10 genera, and four species in the microbiota with densities exceeding 1%. A negative correlation was observed between body fat percentage and the species Faecalibacterium prausnitzii, Bacteroides vulgatus, and the genus Faecalibacterium. In terms of nutrition, fat intake was positively correlated with Actinobacteria and Blautia coccoides; energy and fiber intake were correlated with Prevotella and Prevotella copri. Additionally, carbohydrate intake was negatively correlated with Faecalibacterium.

Given the link between microbiota ccomposition and nutritional intake, uncovered in the previous study [105], microbiomics research can be leveraged to devise personalized nutritional strategies aimed at enhancing and optimizing footballers' performance. For instance, Mancin et al. [106] investigated the effects of consuming 30 g of dark chocolate daily for 4 weeks on blood lipid profiles and gut microbiota composition in elite male soccer players. The participants were randomly assigned to either a dark chocolate group or a white chocolate control group. Blood, fecal samples, and anthropometric data were collected at baseline and after the intervention. The dark chocolate group showed significant improvements in blood lipid profiles, including reductions in total cholesterol, triglycerides, and low-density lipoprotein, along with an increase in high-density lipoprotein. The ratio of arachidonic acid to eicosapentaenoic acid in the blood decreased significantly in the dark chocolate group compared to the white chocolate group, indicating a potential reduction in inflammation. Plasma polyphenol levels increased in the dark chocolate group. Further, gut microbiota in the same group showed slightly higher stability over time, with lower community dissimilarity.

In another study, the same group [107] aimed to assess the influence of a ketogenic Mediterranean diet with phytoextracts (KEMEPHY) on gut microbiome composition in semi-professional soccer players. Sixteen male players were randomly assigned to either a KEMEPHY diet group (n=8) or a Western diet group (n=8). The researchers measured body composition, performance, and gut microbiome composition before and after 30 days using 16S rRNA amplicon sequencing. Alpha diversity measures and PERMANOVA were employed to investigate changes in microbial abundance at various taxonomic levels, and correlations between microbial composition

 doi:10.20944/preprints202410.1705.v1

and macronutrient intake were assessed. The results showed no significant pre- and post-intervention differences in microbial diversity. However, a significant time-group effect was found for the Actinobacteriota phylum, which increased in the Western diet group and decreased in the KEMEPHY diet group. Linear discriminant analysis identified specific genera that distinguished the two diets: Bifidobacterium, Butyricicoccus, and Acidaminococcus were more abundant in the Western diet group, while Clostridia UCG-014, Butyricimonas, Odoribacter, and Ruminococcus were more abundant in the KEMEPHY group.

4.4. Current Limitations of Microbiomics in Soccer Research and Future Directions

While microbiomics research in soccer has yielded promising insights into how gut and oral microbiota affect athletic performance, several limitations remain. The existing studies often involve small sample sizes and short durations, limiting the generalizability of their findings. Moreover, variations in study designs, sequencing methods, and analytical tools can lead to inconsistent results, making it difficult to establish definitive links between microbiota composition and performance outcomes. The complex interactions between diet, training intensity, and microbiota are not fully understood, and confounding factors such as genetics and environmental influences are often not adequately controlled. Additionally, most research focuses on male athletes, leaving a gap in understanding how microbiota affects female soccer players. Future studies should aim for larger, more diverse cohorts with longitudinal designs to explore how microbiota evolves across seasons, injury recoveries, and different training regimens. Advances in multi-omics integration, incorporating metabolomics and proteomics, could provide deeper insights into the mechanistic pathways linking microbiota to performance. Personalized nutrition interventions based on microbiota profiles also hold potential for optimizing player health and recovery, but require more robust clinical trials before being widely implemented in elite soccer.

4.5. Integration of Multi-Omics Data in Soccer

The true strength of Socceromics lies in the integration of multiple omics datasets, which together provide a comprehensive view of an athlete's physiological state. By combining genomics, metabolomics, and proteomics, clubs can gain insights into how players are likely to perform under different conditions, how they recover from injuries, and what specific interventions are most effective for their health (Table 2). Metabolic responses in footballers are, indeed, multifactorial, driven by a combination of dietary intake, physical training, and microbiome interactions [97].

Table 2. Overview of the proteomics, metabolomics, microbiomics, and integrative omics studies related to soccer.

Omics Type	Study Focus	Key Findings	Resarch Examples
Proteomics	Muscle physiology, recovery	Proteins related to inflammation and muscle repair change post-match, indicating recovery needs	Study found changes in alpha-1-antitrypsin and fibrinogen in professional soccer players
Metabolomics	Energy metabolism, recovery	Metabolites such as 3-methylhistidine and taurine associated with muscle breakdown and energy metabolism	Urinary metabolite profiles showed significant changes pre- and post-match in elite soccer players

 doi:10.20944/preprints202410.1705.v1

Microbiomics	Gut microbiota and performance	Increased diversity in gut microbiota correlates with better recovery and performance in elite soccer	Studies revealed that soccer players have more butyrate-producing bacteria, aiding in recovery and energy metabolism
Integrative Omics	Combined impact of multiple omics	Integration of genomic, metabolomic, and proteomic data provides insights into player health and recovery	Integrated analysis showed that combining genomic and metabolic profiles can predict injury risk and optimize training loads

For instance, González et al. [108] explored how genetic data, when integrated with metabolomic and workload data, could predict injuries in elite female footballers. The study identified specific genetic polymorphisms associated with increased risk of muscle and ligament injuries. This kind of research is laying the groundwork for precision medicine in sports, where interventions can be customized based on an athlete's genetic and metabolic profile.

Orrù et al. [109] conducted a study comparing nine lifelong football players (average age 67.3±2.8 years) with nine age-matched untrained individuals. Using proteomic and metabolomic analysis of Vastus lateralis muscle biopsies, the data were processed through various bioinformatic tools. The study found that lifelong football training enhances the oxidative capacity of muscles in elderly individuals by promoting the use of fatty acids as the preferred energy source, leading to healthier body composition and metabolic profiles. Additionally, lifelong football players showed higher levels of polyamines in their muscles, which are associated with muscle growth and hypertrophy. The findings suggest that lifelong football training positively impacts the proteins and metabolites involved in oxidative metabolism and muscle hypertrophy, contributing to healthier aging.

4.6. Current Limitations of Multi-Omics in Soccer Research and Future Directions: Toward Socceromics

The integration of multi-omics data in soccer research holds great promise but faces several limitations that need to be addressed for broader implementation. One major challenge is the complexity and cost associated with generating, managing, and analyzing large multi-omics datasets. Additionally, variations in data collection methodologies, sample handling, and analytical platforms can lead to inconsistencies across studies, hindering the reproducibility and comparability of results. There is also a lack of standardization in how omics data are interpreted and integrated into actionable insights for performance, injury prevention, and recovery strategies. Moreover, most multi-omics research in soccer is conducted in controlled environments, which may not fully capture the dynamic and unpredictable nature of the sport. This can make it difficult to translate findings into real-world applications. Furthermore, much of the current research focuses on male athletes, leaving female athletes underrepresented. Moving forward, it will be essential to standardize data protocols, expand research to include diverse populations, and develop user-friendly tools for coaches and medical staff to apply multi-omics insights in everyday decision-making. Longitudinal studies tracking omics changes over a season, combined with real-time monitoring technologies, will help refine the predictive power of Socceromics, ultimately enabling more personalized and precise interventions for players [110].

5. Discussion

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This study highlights the critical role that omics technologies—genomics, metabolomics, proteomics, and microbiomics—play in enhancing performance, injury prevention, and recovery in elite soccer players. By integrating these approaches, Socceromics aims to provide a comprehensive understanding of how various physiological and molecular profiles influence player outcomes.

The findings of thee studies here reviewed support the growing body of evidence that personalized, data-driven interventions can significantly improve player performance, health, and recovery, offering clubs a strategic advantage in tailoring training programs and recovery protocols. The genomic analysis revealed several genetic markers, such as ACE, ACTN3, and COL1A1, that are associated with key traits like endurance, speed, muscle injury risk, and recovery efficiency. The association of ACE polymorphisms with performance and hypertrophy confirms previous findings in the literature, where the I/D polymorphism has been linked to both endurance and strength traits. Moreover, our results corroborate prior studies that found ACTN3 genotypes to play a pivotal role in speed and injury susceptibility, emphasizing the utility of genomic testing for injury prevention and athlete management. Metabolomic analysis provides insights into the real-time physiological responses of soccer players during and after intense physical activity. The findings of significant changes in metabolites linked to energy metabolism, protein breakdown, and recovery processes align with prior research, which shows that monitoring metabolic fluctuations can optimize training loads and recovery strategies. The identification of fatigue-related metabolites, such as 3-methylhistidine and amino acids, suggests that metabolomics could be a powerful tool for managing player fatigue and preventing overtraining. However, as with many metabolomic studies, variability in sample normalization and the transient nature of certain metabolites may pose challenges for broader application, particularly in a sport as physically variable as soccer. Proteomic analysis provided further validation of muscle physiology and recovery processes, identifying key proteins involved in inflammation and muscle repair. These findings emphasize the importance of monitoring protein biomarkers to assess recovery times and identify potential injury risks. Proteomics can thus be a valuable tool in predicting player readiness, enabling clubs to adjust training loads accordingly and avoid muscle strain injuries, a common issue in professional soccer. The role of microbiomics in soccer, though a relatively new area of research, offers promising avenues for performance enhancement and injury prevention. Our study found significant associations between gut microbiota composition and both physical performance and recovery, underscoring the impact of diet and microbiome health on overall player fitness. These findings are consistent with emerging research that shows a diverse gut microbiota is linked to improved metabolic health and reduced inflammation in athletes. Personalized nutrition strategies based on microbiomic profiles could therefore become an essential component of athlete care, optimizing both performance and recovery.

The integration of multi-omics data in this study illustrates the complexity of elite athletic performance and the importance of a holistic approach to training and recovery. By combining genomic, metabolomic, proteomic, and microbiomic data, we can create a more detailed picture of a player's physiological state, which can be used to tailor interventions for maximal performance and injury prevention. The predictive power of these integrated datasets suggests that future advancements in Socceromics will focus on even more precise interventions, customized to the genetic and metabolic profiles of individual players.

Despite these promising results, this review has several limitations. First, while the integration of multiple omics technologies provides a comprehensive view of athlete physiology, the sample sizes in some of the included studies were relatively small, particularly in the genomic and microbiomic studies. Larger cohorts are necessary to validate these findings and ensure they are generalizable across different populations and playing positions. Additionally, the study primarily focused on male athletes, and future research should aim to include a more diverse group of players, including female athletes, to better understand sex-based differences in omics profiles. Another limitation is the reliance on cross-sectional data, which may not fully capture the dynamic nature of physiological responses to training and competition. Longitudinal studies that track players over entire seasons would offer more insight into how omics profiles change over time and under varying competitive conditions. Additionally, more work is needed to explore the psychological factors that

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influence performance, as these were not addressed in the current study. In conclusion, this study demonstrates the potential of omics technologies to revolutionize the way soccer players are trained, monitored, and managed. By integrating genomics, metabolomics, proteomics, and microbiomics, clubs can better predict performance outcomes, prevent injuries, and optimize recovery. Future research should aim to address current limitations, including the need for larger, more diverse samples and longitudinal data. As Socceromics continues to evolve, the incorporation of advanced technologies such as machine learning and artificial intelligence may further enhance the predictive power of multi-omics data, leading to even more precise and personalized approaches to athlete development.

6. Conclusions

Socceromics, the application of omics technologies in soccer, represents the cutting edge of sports science. By utilizing genomics, metabolomics, proteomics, and microbiomics, clubs can personalize training, recovery, and nutritional strategies to suit the individual needs of each player. The ability to tailor interventions based on biological data offers significant advantages in performance optimization, injury prevention, and recovery management. However, the widespread adoption of Socceromics requires overcoming challenges such as data interpretation, technological costs, and ethical concerns surrounding genetic privacy. Despite these challenges, the integration of omics technologies is set to revolutionize how soccer players are trained and managed, providing a foundation for more efficient, data-driven sports management in the years to come.

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