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Physical activity and gene association with human obesity

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Abstract

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Keywords

sport genetics; obesity; physical activity; polymorphisms; adaptation

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REVIEW

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Physical activity and gene association with human obesity

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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abstract

The obesity is a leading cause of health problems all over the world. It is a comlex health abnormality that is influenced by developmental, behavioural, environmental, and genetic factors. Although the role of physical activity and diet in regulation of body weight is well described, the genetic variants potentially influencing the characteristics and range of the body's adaptive response to physical activity in healthy individuals still remains mostly unknown. The main aim of this study is to review current evidence, through a literature review and the results of our studies, on the influence of selected molecular markers on the development of obesity, as well as the body composition changes in response to regular physical activity. We studied the most reliable candidate genes with a focus on catechol-O-methyltransferase gene (*COMT*), dopamine deceptor D2 gene (*DRD2*), fatty acid binding protein 2 gene (*FABP2*), fat mass and obesity-associated gene (*FTO*), and uncoupling protein 1 (*UCP-1*). This review provides information about recent genetic research progressions in adiposity, as well as molecular mechanisms, associated phenotypes, as well as their implications for human health, physical performance, and adaptive changes in response to physical activity.

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INTRODUCTION

Human obesity and overweight have been considered as a worldwide epidemic [1]. These days excessive body weight gain is defined as a civilization disease and has become one of the largest public health problems [2], since nearly 40% of adults are overweight and 10–15% are obese all over the world [3].

The World Health Organisation (WHO) has defined obesity in adults as the body mass index (BMI) of ≥30 kg/m^2 and overweight as the BMI between 25 and 30 kg/m^2 [4]. According to scientists, the higher the BMI, the greater the risk of many medical problems. Its relationship with the occurrence of cardiovascular diseases (CVD), such as hypertension and coronary hearts diseases, as well as type 2 diabetes (T2D), lipid disorders, some types of cancer, and overall mortality has been confirmed [5, 6]. Moreover, a high BMI is also associated with infertility [7], which mainly concerns ovulatory disorders in the case of women [8, 9].

However, measurement of BMI has some limitations, since it takes into account only two parameters: a person's weight and height. This parameter cannot show the extent of adipose tissue (AT) in different individuals. The prevalence of percentage AT is different depending on gender, age, and ethnic origin. For instance, women have more subcutaneous adipose tissue (SAT), while men have fat, predominantly distributed to the visceral adipose tissue (VAT) around the abdominal organs creating abdominal obesity [10–12]. When it comes to the ethnic origin, Africans especially African women tend to be more obese and have a different body fat distribution than European woman [13, 14].

As mentioned, BMI does not measure AT directly; on the other hand, some studies have shown that BMI is partly correlated with more direct measures of body fat obtained from skinfold thickness measurements, bioelectrical impedance, underwater weighing, dual energy x-ray absorptiometry (DXA), and other methods [15–16].

Abdominal obesity is also known as visceral obesity, which refers to VAT. This parameter was recognised by the WHO in 1997 in order to perfect BMI. Waist circumference (WC) is a measure of abdominal obesity and is associated with all-cause mortality [17–18]. Furthermore, recent studies have shown that visceral obesity is increasing at an even higher rate than general obesity [19].

According to many studies, developmental, behavioural, environmental, and/or genetic factors have been considered an integral component of weight management and have an influence on future morbidity [20]. Physical activity (PA) is the most crucial factor in order to maintain appropriate body weight as per WHO statement. What is more, the benefits of PA are considered as effective prophylactic in regard to preventing CVD and many other medical problems [21]. Low PA among adults can lead to a higher prevalence of metabolic disorders such as heart disease, hypertension, T2D, and some cancers [22–23]. According to the recent studies, parental PA plays a positive role in modulation of the progeny's phenotype of their children. Interestingly, both the mothers' and fathers' PA – before their child is conceived – may be one of the appropriate way to potentially improve their progeny's health [24–25]. Current evidence demonstrates the protective effect of the parents' training/exercise on their progeny in relation to the general prevention of chronic diseases, including human obesity, T2D, and hypertension [26].

In addition, environmental and genetic factors are highly associated with human obesity. They play a key role in the regulation of body weight, since there are genes involved in control of energy consumption and expenditure, lipid and carbohydrates metabolism, adipogenesis, thermogenesis, as well as cell differentiation [27]. The heritability of BMI, which is defined as proportion of inter-individual variation attributable to genetic factors, has been estimated

to be 40–70% [28]. In addition, more than 600 genes and chromosomal regions have been characterised to take part in body weight and energy metabolism regulation [27]. The most reliable molecular markers are presented in Table 1.

Table 1. Molecular markers associated with human obesity and effectiveness of exercise training programmes

Gene	Chromosome location	Gene product	Polymorphism	Risk allele
beta-2 adrenergic receptor gene, *ADRB2*	5q31–32	beta-2 adrenergic receptor	rs1042713, G/A	G
brain-derived neurotrophic factor gene, *BDNF*	11p14.1	brain-derived neurotrophic factor	rs10767664, A/T	T
cordon-bleu protein like 1 gene, *COBLL1*	2q24.3	cordon-bleu protein like 1	rs7607980, T/C	C
catechol-O-methyltransferase gene, *COMT*	22q11.21	catechol-O-methyltransferase	rs4680, G/A, Met/Met	Met
D2 dopamine receptor gene, *DRD2*	11q23.2	dopamine D2 receptor	rs1800497, G/A, Taq1A	A1
fatty acid binding protein 2 gene, *FABP2*	4q28-4q31	fatty acid binding protein 2	rs1799883, G/A, Ala54Thr	Thr54
fat mass and obesity-associated gene, *FTO*	16q12.2	a nuclear protein - 2-oxoglutarate (2-OG) Fe(II) dependent demethylase	rs9939609, A/T	A
glucosamine-6-phosphate deaminase 2 gene, *GNPDA2*	4p12	glucosamine-6-phosphate deaminase 2	rs10938397, G/A	G
insulin receptor substrate 1 gene, *IRS1*	2q36.3	insulin receptor substrate 1	rs2943650, C/T	C
potassium channel tetramerization domain containing 15 gene, *KCTD15*	19q13.11	potassium channel tetramerization domain containing 15	rs29941, C/T	C
leptin gene, *LEP*	7q31and 1p31	leptin	rs2167270, G/A	A
leptin receptor gene, *LEPR*	7q31and 1p31	leptin receptor	rs1137101, G/A	G
melanocortin-3 receptor gene, *MC3R*	20q13.2	melanocortin-3 receptor	rs3746619, A/C	A
melanocortin-4 receptor gene, *MC4R*	18q21.32	melanocortin-4 receptor	rs17782313, C/T	C
mitochondrial carrier homolog 2 gene, *MTCH2*	11p11.2	mitochondrial carrier homolog 2	rs3817334, C/T	T
methylenetetrahydrofolate reductase gene, *MTHFR*	1p36.22	methylenetetrahydrofolate reductase	rs1801133, C/T	T
methionine synthase reductase gene, *MTRR*	5p15.31	methionine synthase reductase	rs1802059, A/G	A
neuronal growth regulator 1 gene, *NEGR1*	1p31.1.	neuronal growth regulator 1	rs2815752, G/A	A
pro-opiomelanocortin gene, *POMC*	2p23. 3	pro-opiomelanocortin	rs2071345, C/T	T
proliferator-activated receptor-gamma gene, *PPARG*	3p25.2	proliferator-activated receptor-gamma	rs1801282, C/G	C
transmembrane protein 18 gene, *TMEM18*	2p25.3	transmembrane protein 18	rs6548238, C/T	C
uncoupling protein 1 gene, *UCP1*	4q31.1	uncoupling protein 1	rs3811791, C/C	C
uncoupling protein 3 gene, *UCP3*	11q13.4	transmembrane protein 18	rs6548238, C/T	C

There are three types of human obesity correlated with genes. Monogenic obesity is described as rare and severe early-onset obesity with abnormal feeding behaviour and endocrine disorders. The influence of genetics is enormous and only little dependent on environmental factors. This form of obesity is mainly due to mutations in genes of the leptin/melanocortin axis involved in food intake regulation. Among the genes associated with the development of

monogenic obesity, e.g. leptin (*LEP*) and leptin receptor (*LEPR*), proopiomelanocortin (*POMC*), and proconvertase 1 (*PC1*) can be distinguished. This type of adiposity involves only 2–3% of obese children and adults [29].

Syndromic obesity is associated with mental retardation, dysmorphic features, and organ-specific developmental abnormalities. This type of obesity is responsible for 2% of obesity in adults and children [30].

The last but not least type of adiposity related to genes is polygenic obesity. This kind of obesity includes about 95% cases and according to many studies is highly associated with environmental factors, such as low physical activity, excessive caloric intake, the intrauterine environment, medications, socioeconomic status, and possibly novel factors, such as insufficient sleep, endocrine disruptors, and the gastrointestinal microbiome [31]. Although the mentioned factors are quite well described in the development of obesity, the genetic background still remains mostly unknown. Additionally, only a few polymorphisms have been described in the context of their potential influence on the extent and the nature of the response to training in healthy and obesity individuals [32].

The main aim of this study is to review current evidence, through a literature review and the results of our studies, on the influence of gene variants on the development of obesity, as well as on characteristics and range of the body's adaptive response to training. We studied the most reliable candi¬date genetic markers with a focus on catechol-O-methyltransferase gene (*COMT*), dopamine receptor D2 gene (*DRD2*), fatty acid binding protein 2 gene (*FABP2*), fat mass and obesity-associated gene (*FTO*), and uncoupling protein 1 (*UCP-1*). This review provides information about recent genetic research progressions in adiposity, as well as molecular mechanisms, associated phenotypes, as well as their implications for human health, physical performance, and adaptive changes in response to physical activity.

COMT

The *COMT* gene is located on the long arm of chromosome 22 and encodes catechol-O-methyltransferase, which is a major regulator of dopaminergic and adrenergic neurotransmission. The COMT enzyme transfers a methyl group from S-adenosyl-L-methionine (SAM) to one of the catecholic hydroxyls, which has a role in inactivation of catecholamine neurotransmitters and catechol hormones such as dopamine (DA) [33]. Two isoforms are distinguished: the soluble form (S-COMT) and the membrane-bound form (MB-COMT). The second one is expressed mostly in brain neurons and is engaged in the control of extracellular DA levels in the prefrontal cortex. It has been demonstrated to be involved in neuropsychiatric disorders and neurobiology of cognition, emotions, behaviour, sleep regulation, pain processing and perception, addictive behaviour, and neurodegeneration [33–35]. In result, the enzyme's activity may also play a crucial role in the development of sport abilities.

The main cause of variation in the enzyme's activity is a common single nucleotide polymorphism (SNP) within the coding region of the *COMT* gene involving a G to A transition, resulting in the substitution of valine for methionine (Val158Met; rs4680). The presence of the Met allele has been shown to reduce the activity of COMT, because of its higher thermolability, which in turn increases the DA levels [36].

In a study including 57 Asian elite athletes, Abe et al. [37] examined the interaction between the SNPs influencing DA system functions and swimmers' competitive performance. They noted an effect of the rs4680 polymorphism on a swimmer's competitive performance. The Met allele carriers demonstrated a higher mean value of FINA points and were more often elite athletes than the Val allele carriers. They proposed that swimmers with the Met allele

might achieve outstanding sports results under high pressure due to their superior executive control. Another study performed on 75 participants undergoing 17 weeks of running training demonstrated that individuals with the Val/Val genotype demonstrated greater executive control abilities after aerobic exercise training than the Met allele carriers. It was assumed that an increase in physical fitness causes improved cognitive functioning via dopaminergic modulation [38]. Abe et al. [37] suggested that improving the athletic performance of Val/Val swimmers might be possible by applying an exhaustive training to improve aerobic capacity. However, the results obtained by Zmijewski et al. did not confirm significant differences in the genotype distributions or allele frequencies between in elite short- and long-distance swimmers, as well as sedentary controls [39].

In addition, the *COMT* Val158Met polymorphism was associated with baseline fat measures and seemed to alter the effect of the exercise intervention on fat loss in a group of 173 postmenopausal women. It was found that carriers of the Met/Met genotype had higher baseline fat levels and lost less fat after an exercise intervention (225 min/wk of moderate-intensity exercise for one year) compared with carriers of the Val/Val genotype [40]. Witte et al. also show significant interactions of the *COMT* genotype and dietary intervention with regard to cognition. A better cognitive response to dietary interventions for the Val/Val genotype carriers compared to carriers of one or two the Met-alleles was described [41].

DRD2

Dopamine (DA; 3,4-dihydroxy-phenylethylamine) is an essential catecholamine neurotransmitter that regulates multiple physiological and cognitive functions including the development of fatigue, which leads to a decrease in an intensity or interruption of exercise, through modulation circuits linked to the motor control and thermoregulatory, as well as motivation and reward systems [42–44]. The physiological roles of DA were first described in 1958 [34]. The first evidence of the association between DA and exercise dates from the 1970s and the 1980s in studies with rats which suggested that the DA signal system may be associated with physical activity-related behaviours [45–47]. DA activity mainly depends on DA receptors density and function [48]. There have been identified five DA receptors among humans: DRD1, DRD2, DRD3, DRD4, DRD5 [49], which are mostly present in the central nervous system specifically in the hippocampal dentate gyrus and subventricular zone. DA receptors are also expressed in the periphery, more prominently in kidneys and the vasculature [50–51].

The most likely candidate gene of DA system associated with individual differences in cognitive abilities which may underlie differences in achieving remarkable results in professional sports competition and everyday physical activity is the *DRD2* gene. It is located on chromosome 11, contains 8 exons and 6 introns, and spans 65,56 kb [52]. The *DRD2* gene is probably regulated by ankyrin repeat and kinase domain containing 1 gene (*ANKK1*) through Nuclear Factor-kappaB (NF-kB). Genetic variations in *DRD2* can alter dopamine signalling and modify the rewarding effects of food; moreover, some studies investigated the association of the *DRD2* polymorphisms with BMI and hedonic hunger [53], since dopamine plays an important role in the regulation of appetite and the growth hormone [54–55]. Furthermore, variations in the FTO gene are the strongest polygenic determinants of obesity [56], and inactivation of this gene impairs *DRD2*-dependent neurotransmission and function in rodents [57].

SNP located in *DRD2*, the insertion (Ins) or the deletion (Del) of cytosine (C) in the promoter region of the gene at position -141 (-141C Ins/Del; rs1799732) [58] has been linked to BMI and hedonic hunger. The -141C Del allele produces lower expression of *DRD2*. The -141C Ins/Del allele has been related with reduced promoter activity which effects the decreased protein expression [59]. Aliasghari et al. found significant differences in the allele frequencies of this polymorphism between the overweight/obese and normal weight controls. The frequency of Del (rs1799732) allele was higher in overweight/obese individuals [60].

The Taq1A polymorphism (G/A, rs1800497) has been most frequently studied polymorphism of *DRD2*. The A1 allele of this polymorphism has been associated with reduced *DRD2* density in the striatum, decreased reward sensitivity, and reduction in novelty-seeking behaviour. For instance, Wang et al. found that those with lower D2 receptor densities in the striatum were more likely to be obese [61]. Pohjalainen et al. indicated that individuals who possess A1 allele of *DRD2* are more often addicted to exercise since possession of A1 allele is significantly associated with lower *DRD2* expression [62]. What is more, this study has shown possession of the A1 allele of *DRD2* may play a significant role in the process of PA addiction among male participants, hence exercise addiction may play a key role in preventing having of other addictive behaviours (e.g. binge eating disorder, BED) among male participants who possess the A1 allele of *DRD2* [63].

Cameron et al. also established that the TaqIA genotype was associated with body weight loss, fat mass loss, and a decrease in BMI post-intervention in a group of obese postmenopausal women. Specifically, carriers of the A1 allele exhibited smaller reductions in body weight, fat mass, and BMI pre- and post-intervention in a group of women who entered a combined 6-month resistance training program and caloric restriction intervention, whereas no interactive effects were found in a group of women only limiting calories [64].

FABP2

One of the most promising candidate genetic markers is *FABP2* [65]. The gene is located in the long arm of chromosome 4 and encoded an intracellular protein which is a member of the FABPs superfamily [66]. The intestinal FABP2 binds saturated and unsaturated long-chain fatty acids and is involved in the synthesis of triglyceride-rich lipoproteins. In addition, the gene product takes part in the absorption, intracellular transport, and metabolism of dietary fatty acids and their acyl-CoA esters in small intestine [67–69]. Thus, the *FABP2* is an extensively studied candidate gene related to metabolic disorders including obesity, diabetes, and metabolic syndrome [67–68,70–72].

In 1995, a nucleotide transition from G to A at codon 54 in exon 2 of the *FABP2* gene that results in an alanine (Ala) to a threonine (Thr) change (Ala54Thr; rs1799883) was described [67]. Many studies have shown that this missense variation is strongly associated with lipid and carbohydrates metabolism [67-68]. The carriers of the Thr54 variant of *FABP2* have nearly twice the affinity for long-chain fatty acids than those with the Ala54 allele. This evidence supports the potential role of the *FABP2* Ala54Thr polymorphism in the aetiology of human overweight and obesity [67, 73]. Recently, a sexual dimorphism regarding BMI was described for the polymorphism [70, 73].

Although the association between the Ala54Th SNP and excess body mass is well confirmed, the gene × physical activity interaction and its connection with the athlete status is not clear. Nasibulina et al. suggested that while the excess absorption of long-chain fatty acids during sedentary state is considered as a risk factor for overweight and obesity, among athletes this condition can give additional benefit for endurance performance [74]. Indeed, they revealed that the Thr54 allele frequency was higher in elite Russian endurance and combat athletes compared to controls (32.2%). A previous study also showed that higher availability of free fatty acids can provide for enhanced oxidative potential as evidenced by an increase in VO_2max and a decreased running time in trained runners [75].

Our earlier findings confirm that the carriers of the Thr54 allele had higher BMI compared with the Ala54 carriers, suggesting that the Thr54 variant is a risk allele engaged in excess body mass in Polish women. On the other hand, we did not found evidence of a relationship between the *FABP2* Ala54Thr polymorphism and physical activity on the selected body mass

measurements as well as with biochemical parameters [76]. These results are consistent with Han [81], who showed that a 12-week regular aerobic training can beneficially prevent obesity-related traits; however, none of the examined parameters significantly changed across the *FABP2* genotypes [81]. Furthermore, total cholesterol, high-density lipoprotein (HDL), and triglycerides (TGL) levels were not significantly changed by the joint effects of the genotypes and cardiorespiratory fitness in 837 participants from Japan [77].

FTO

In 2007, three different research groups have revealed that a group of polymorphisms in the first intron of *FTO* is related to body mass and body composition parameters, such as BMI, hip circumference, total body weight, body fat percentage, and cardiometabolic traits [78–80]. As a result, it has been associated with overweight and obesity risk among numerous ethnic populations as well as various age groups [81–84].

The human *FTO* gene is localized to long arm of chromosome 16 and encodes a 2-oxoglutarate (2-OG) Fe (II) dependent demethylase [78, 89]. *FTO* is a nuclear protein which is able to remove methyl groups from 3-methylthymine in single-stranded DNA, as well as 3-methyluracil and 6-methyladenosine in single-stranded RNA nucleotides [85]. Thus, the gene product is involved in regulation of genes transcription and posttranslational modifications, as well as repair and/or modification of nucleic acid by demethylation [82, 85]. It was suggested that this nuclear protein can regulate the pathways controlling e.g. food intake, nutrient preference, appetite and satiety, as well as control over eating [82].

A/T polymorphism (rs9939609), which is most often described in the context of obesity-related traits, is located in the first intron of the *FTO* gene. It was suggested to play an important role in the regulation of transcription, either to up- or down-regulate the *FTO* expression [80]. The A allele was characterized as a risk allele, because it is related to 20%–30% higher risk of overweight and obesity. Frayling and colleagues showed that ~16% of the examined populations are the AA homozygous, and these persons weigh ~3 kg more when compared with the TT homozygous [78].

So far, only a few studies have tried to clarify the association between the *FTO* A/T polymorphism and sport predispositions or training-induced changes in athletes and sedentary individuals. In the study comparing 1089 participants, Heffernan et al. [86] suggested that the T allele is associated with increased body lean mass, muscle-related phenotypes, as well as elite athletic status. These results were confirmed by Guilherme et al. [87] who established that the *FTO* AA genotype is less frequent in Brazilian (n=677) and Russian (n=920) athletes more reliant on a lean phenotype and linked to a reduced proportion of slow-twitch muscle fibres, while it is over-represented in power and combat sport athletes of heavier weight categories. Additionally, a lower frequency of the AA and the AT genotype, as well as the A allele among elite Polish swimmers, was shown implying that some people may benefit from carrying the T allele. The TT homozygous person had 1.5–2.0 times higher chance of being an elite swimmer [86]. However, Eynon et al. [89] did not demonstrate a connection between the A/T polymorphism and the elite athlete status in the group of Spanish (n=81), Polish (n=214), and Russian (n=256) athletes.

A large-scale meta-analysis revealed that the *FTO* effect on the risk of excess of body mass is ~30% lower in physically active persons than in people leading a sedentary lifestyle [90]. These observations were confirmed by Li et al. who showed that living a physically active lifestyle is linked to a 40% reduction in the genetic predisposition to overweight and obesity [91]. In other studies, the effect size of the *FTO* polymorphisms was as much as 80% lower in physically active people [92–93]. However, not all studies have demonstrated the gene ×

physical activity interaction [94–95]. Although a study conducted on 201 healthy Caucasian women confirmed an association between the AA and AT genotypes and higher BMI, the gene × physical activity interaction was not shown [95].

UCP1

The human *UCP-1* gene is located on a long arm of chromosome 4, spans 13 kb and contains a transcribed region that covers 9 kb [96–97]. The gene product is located in the inner mitochondrial membrane mainly in brown adipose tissue (BAT), in which UCP1 allows protons to re-enter the matrix, bypassing the adenosine triphosphate (ATP) synthase [98]. *UCP1* expression is highly induced when thermogenesis is required [99]. It was recently shown that mRNA and/or protein were detected not only in BAT but also in the white adipose tissue (WAT) [100–101], skeletal muscle [102], and longitudinal smooth muscle layers [103]. UCP1 plays a significant role in thermogenesis and energy expenditure; therefore, it has an influence on the pathogenesis of obesity and metabolic disorders in human [104–107].

Oppert et al. revealed that frequent A/G substitution at position -3826 upstream of the *UCP1* gene (A-3826G, rs1800592) was associated with human obesity and weight gain in 261 Canadians. This was the first study to find a dependence between higher BMI and the G variant of UCP-1 in Canadians [108]. Until now, many association studies were conducted in various populations to explain the association of the A-3826G polymorphism with obesity phenotypes, T2D, and lipid/lipoprotein-related disease [108, 109–110].

Although, Kieć-Wilk et al. implied that UCP1 does not play a major role in the development of obesity and/or disturbances of glucose metabolism, in a study including 118 overweight and obese patients from Poland, they revealed increased levels of triglyceride (TG) and free fatty acids (FFA) and decreased levels of high-density lipoprotein (HDL) observed in carriers of the G allele. It was suggested that FFA-induced impairment of the HDL turnover and disturbance of the β-cell function, which are important risk factors for endothelial injury [111]. In addition, in a study including 113 Japanese obese participants who were treated with a combined low-calorie diet and exercise for 3 months, Kogure et al. showed that a decrease in the body weight was lower in the G allele carriers than in the A allele carriers, whereas the food intake, exercise, and initial BMI were similar in both groups [112]. These results confirmed previous data which indicated that the genetic variant of UCP1 is associated with resistance to low-calorie diet, suggesting a role of UCP1 and BAT in the body weight regulation in humans [113].

CONCLUSIONS

Regular PA plays a key role in maintaining not only appropriate body weight but also body composition such as adipose and muscle tissue [114]. There are many reasons why greater PA is required to maintain an appropriate body weight. First of all, the current food environment encourages excess caloric intake and positive energy balance. Interestingly, the lifestyle during non-leisure PA has become increasingly sedentary, a trend that will continue [115]. Systematic PA is also associated with many health-related benefits, including a reduced risk of developing several chronic diseases such as CAD, T2D, metabolic syndrome (MS), and cancer. Even light-intensity PA may be associated with blood glucose reductions, whereas sedentary time may be unfavourably associated with its increased levels [116]. Additionally, genetic factors play a fundamental role in the regulation of body weight and body composition, since there are genes involved in regulation of energy expenditure, carbohydrates and lipid metabolism, appetite, thermogenesis, adipogenesis, as well as cell apoptosis and differentiation [32].

A genome-wide association studies (GWASs) have identified many SNPs in *FTO* and other genes such as, *COMT*, *DRD2*, *FABP2*, *FTO*, *LEP*, *LEPR*, *MC4R*, *POMC*, *UCP1* [117–119] that

are associated with the risk of developing obesity. Among these genes, *FTO* has been reported as the gene with the strongest correlation with adiposity [120–121]. However, the majority of identified gene variants have unknown biological functions and some of these studies yielded contradictory results, suggesting a need for further research into the functions of identified polymorphisms referred to adiposity. Additionally, only few SNPs have been described in the context of their potential effect on the extent and nature of the response to training program in healthy individuals from different populations [32, 91, 122]. Therefore, more replication studies are required in order to establish the role of the gene variants in the characteristics and range of the body's adaptive response to training and, consequently, to reducing the risk of obesity in the next generation. Understanding the genetics of biochemical and physiological processes would have a wide impact on individualization of training programs to be more effective and safer, improved recovery, medical care, traumatology, nutrition, supplementation, and many other fields.

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