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Genetic variants influencing effectiveness of exercise training programmes in obesity – an overview of human studies

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ABSTRACT: Frequent and regular physical activity has significant benefits for health, including improvement of body composition and help in weight control. Consequently, promoting training programmes, particularly in those who are genetically predisposed, is a significant step towards controlling the presently increasing epidemic of obesity. Although the physiological responses of the human body to exercise are quite well described, the genetic background of these reactions still remains mostly unknown. This review not only summarizes the current evidence, through a literature review and the results of our studies on the influence of gene variants on the characteristics and range of the body's adaptive response to training, but also explores research organization problems, future trends, and possibilities. We describe the most reliable candidate genetic markers that are involved in energy balance pathways and body composition changes in response to training programmes, such as *FTO, MC4R, ACE, PPARG, LEP, LEPR, ADRB2,* and *ADRB3*. This knowledge can have an enormous impact not only on individualization of exercise programmes to make them more efficient and safer, but also on improved recovery, traumatology, medical care, diet, supplementation and many other areas. Nevertheless, the current studies still represent only the first steps towards a better understanding of the genetic factors that influence obesity-related traits, as well as gene variant x physical activity interactions, so further research is necessary.

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INTRODUCTION

Regular physical activity has significant benefits for human health, including reduction of the risk of cardiovascular diseases, type 2 diabetes and certain forms of cancer, and improvement of mental health. Additionally, properly selected exercises are a key component of the total daily energy expenditure and as such contribute to improved body composition and help control weight [1]. Currently, the number of people with overweight and obesity is increasing rapidly worldwide and is described as an epidemic; consequently, the prevention of weight gain is a very important health issue [2].

Excessive body weight gain because of an increase in adipose tissue is the consequence of an imbalance between energy consumption and energy expenditure. The imbalance can be affected by both caloric intake and physical activity, which may be dependent on developmental, behavioural, and/or environmental factors [3]. Additionally, genetic factors play a fundamental role in the regulation of body weight, since there are genes involved in regulation of energy expenditure, appetite, lipid metabolism, adipogenesis, thermogenesis, and cell differentiation [4]. The reported heritability of body mass index (BMI) ranges from 40% to as high as 70% [5,6]. However, Li et al. [7] revealed that leading a physically active lifestyle is associated with a 40% reduction of the genetic predisposition to obesity and emphasized the importance of exercise in prevention of excess body weight. As a consequence, promoting exercise training programmes, particularly in those who are genetically predisposed, is a significant step towards controlling the presently increasing epidemic of obesity [7, 8].

Decades of physiological research in physical activity have resulted in relatively good knowledge of the functional response of the human body to exercise. Although the physiological reactions in the human body after regular exercises are quite well described, the genetic background of these reactions still remains mostly unknown [9]. The process of exercise-induced adaptation in the human body involves a number of signalling mechanisms, initiating replication of specific DNA sequences, enabling their subsequent translation,

and finally generating new proteins. The physiological effects of these adaptations are determined by the volume, intensity and frequency of physical activity [10]. It is well known that individuals vary in their responses to similar training: from a lack of adaptive response to extreme overload. Recent studies have shown that people with the same genotypes respond similarly to exercises in comparison to those with different genotypes, indicating that some genes play a key role in determination of individual differences in response to physical activities. An understanding of the genetic determinants will allow us to clarify the criteria of physical activities for individuals. In the future, this knowledge should help to identify persons who are expected to respond well or poorly to exercise, thus making training programmes much more efficient (allowing accurate prediction of the training results including weight loss and improved health) and safer (allowing early prevention of possible overload, injuries, cardiomyopathies, sudden death, etc.) [9].

Initially, studies performed in families, adoptees, and twins clearly showed a genetic contribution to obesity. However, they did not offer insight into the specific gene variation underlying heritable traits. The era of genetic analyses started in the early 2000s after the development of molecular biological methods, which have enabled researchers to apply genome-wide association studies (GWASs) to the field [11]. GWASs allow for the analysis of polymorphic sites of the whole genome to link genetic markers, usually single-nucleotide polymorphisms (SNPs), to physiological traits [12,13]. More than 600 genes and chromosomal regions have been described to take part in body weight and energy metabolism regulation [4]. Some papers focusing on physical activity behaviour and exercise intolerance, muscular strength and power, cardiorespiratory fitness and endurance performance, body weight and adiposity, glucose and insulin metabolism phenotypes, lipid and lipoprotein metabolism, and hemodynamic traits have revealed candidate genetic markers that are involved in changes of obesity-related traits in response to training programmes [14]. However, only a few polymorphisms have been described in the context of their potential impact on the extent and nature of the response to training in healthy individuals [7,8,15]. It needs to be highlighted that the search for genetic markers of functional responses of the human body to physical activities with the whole-genome approach is certainly more productive than the single-marker case-control and cross-sectional association studies popular so far [16].

This review not only summarizes the current evidence, through a literature review and the results of our studies on the influence of gene variants on the characteristics and range of the body's adaptive response to training, but also explores research organization problems, future trends, and possibilities. We studied the most reliable candidate genetic markers that are involved in energy balance pathways and body composition changes in response to training programmes.

FTO gene

The first described and found by GWAS obesity-susceptibility gene, with the largest influence on higher BMI to date, was the fat mass and obesity-associated gene (*FTO*) [17, 18]. Recently, studies concerning the relationship between *FTO* and weight have been frequently replicated, not only for BMI, but also for obesity risk, body fat percentage, waist circumference, type 2 diabetes, and other types of obesity-related traits. Subsequently, these associations were found to be replicable across different age groups, as well as multiple ethnic populations [19]. Currently, a common *FTO* A/T polymorphism (rs9939609) is one of the most frequently investigated genetic variants in the context of genetic conditioning for a predisposition to body weight excess.

The human *FTO* gene is located in chromosome region 16q12.2 [17], and the product of the gene is the nuclear protein 2-oxoglutarate (2-OG) Fe(II) dependent demethylase [20]. The results so far have established that the enzyme is able to remove methyl groups from DNA and RNA nucleotides *in vitro* with the highest affinity for single stranded RNA molecules [20, 21]. It was suggested that the *FTO* gene can influence the activity of pathways controlling daily food intake, as well as nutrient preference [20].

The *FTO* A/T polymorphism is located in the first intron of the gene, which is associated with an enhanced risk of excessive weight gain, increasing the risk by 20-30%. It was found that carriage of one or two copies of the A allele (risk allele) is associated with average increases in body mass of 1.2 and 3.0 kg, respectively [17]. Numerous studies have shown that the *FTO* effect on obesity-related traits is reduced by approximately 30% in physically active compared to sedentary adults [7, 8, 20, 22]. In other studies, the effect size of *FTO* variants is up to 80% lower in physically active individuals [23, 24]. It was also found that the risk allele (rs9939609 A) of the *FTO* gene was not associated with the low ability to become an elite athlete in any sport [25]. However, not all studies have demonstrated the gene x physical activity interaction [26, 27, 28]. Although our results confirm the association between the common *FTO* A/T polymorphism and increased BMI, none of the examined obesity-related parameters changed significantly across the *FTO* genotypes during a 12-week training programme (unpublished data).

MC4R gene

The melanocortin-4 receptor (*MC4R*) gene encodes a 332-amino-acid protein, which belongs to a family of seven trans-membrane G-protein-coupled receptors (GPCR). The protein is a well-known major regulator of food intake and energy expenditure [29]. Polymorphisms within the *MC4R* coding region have been reported to be associated with obesity in humans [29]. In addition, variants outside of the coding region probably influence its expression and have been associated with a predisposition to excess body weight [30]. GWAS conducted in Caucasians revealed that the variant rs17782313 (C/T polymorphism), mapped 188 kb downstream of the *MC4R* gene [31], also shows a strong association with obesity-related traits [32]. This association has been confirmed in multiple populations including children, adolescents and adults [19, 32].

The risk allele (C) is connected with increased intakes of total energy and dietary fat, and as a result higher prevalence of obesity [33]. Each copy of the C allele is linked with an increase in BMI of ~0.22 kg/m^2 in adults [31]. What is more, the risk allele was also associated with an average 14% increased risk of type 2 diabetes [33]. It has been reported that the effect of the gene on obesity-related traits may be reduced by leading a physically active lifestyle. Li et al. [7] genotyped 12 SNPs in obesity-susceptibility loci including rs17782313 in a group of 20,430 European participants, and found that genetic predisposition to increased BMI and obesity is attenuated by a physically active lifestyle. However, another study did not show an association between the polymorphism and selected body composition measurements in 242 participants undergoing a 9-month lifestyle intervention [34]. In a study performed on 111,421 adults of European descent, Ahmad et al. [8] analyzed 12 loci connected with obesity-related traits and also did not reveal evidence of rs17782313 x physical activity interactions. Additionally, we did not observe interaction of the near-*MC4R* C/T polymorphism with physical activity in a group of 201 Polish women taking part in a 12-week training programme [35].

ACE gene

Nowadays, the angiotensin-converting enzyme gene (*ACE*) is the most frequently investigated genetic marker in the context of genetic conditioning of athletic predispositions. The polymorphism has been associated with improvements in performance and exercise duration in a variety of populations [36]. The gene was also studied in the context of obesity-related traits, type 2 diabetes and hypertension [37]. The product of *ACE* enhances regulatory function in circulatory homeostasis, through the synthesis of vasoconstrictor angiotensin II, which also drives aldosterone synthesis, and the degradation of vasodilator kinins. *ACE* is also expressed in skeletal muscles, where it affects their biomechanical properties [38,39,40]. The gene is situated on chromosome 17 at position 17q23.3, with a polymorphism consisting of the presence (insertion, allele I) or absence (deletion, allele D) of a 287 base pair Alu repeat sequence in intron 16 [41,42]. In this case, the three *ACE* genotypes comprise DD and II homozygotes and ID heterozygotes [43].

Numerous studies concerning the association between the *ACE* genotype and athlete status have shown that the I allele is linked to lower ACE activity in both serum and tissue compared with the D allele [44]. Consequently, the II genotype is associated with improvement in endurance sports while the DD genotype provides an advantage for sports requiring sprinting or short bursts of power [38]. The *ACE* gene is also one of the most frequently investigated genetic markers of a functional response of the human body to physical activities. Moran et al. [45] established that carrying the D allele was associated with increased fat thickness in women with no extra exercise. Some studies have found that the I allele may effectively enhance the efficiency of skeletal muscle after aerobic training. Cam et al. [46] observed that after aerobic training women with the II genotype had significantly better results during the 30-minute run and more favourable changes in physiological parameters than women undergoing the same training programme but with the DD genotype. On the other hand, an increase in muscle strength in individuals with the D allele after anaerobic exercise has been observed [47,48]. In conclusion, the II genotype may be associated with greater improvements in medium duration aerobic endurance performance, whereas the DD genotype seems to be more advantageous in performance enhancement in shorter duration and higher intensity endurance activities [46]. However, our results did not show an association between the *ACE* I/D polymorphism and 12-week physical activity in a group of 201 young women (unpublished data).

Genes of the PPAR family

The peroxisome proliferator-activated receptors genes (PPAR) are frequently investigated genetic markers in the context of athletic predisposition and health-related fitness phenotypes [49] due to the multiple physiological roles of proteins encoded by them [50]. PPAR proteins are lipid-activated nuclear receptors which are members of the nuclear hormone receptor superfamily [51]. The transcriptional activity of PPARs is mediated by PPAR retinoid X receptor (RXR) heterodimers which bind to specific DNA sequence elements termed PPREs (PPAR response elements) in their target genes' regulatory region. The major role of PPARs is the transcriptional regulation of proteins involved in lipid and carbohydrate metabolism. Additionally, PPARs affect expression of genes active in vascular biology, tissue repair, cell proliferation and differentiation [52]. Three PPAR isotypes have been described so far, which exhibit different tissue distribution and functions and, to some extent, different ligand specificities: i) PPARα encoded by the *PPARA* gene located on chromosome 22, ii) PPARδ (also called PPARβ) encoded by the *PPARD* gene on chromosome 6 and iii) PPARγ encoded by the *PPARG* gene on chromosome 3 [50].

The PPAR genes due to their role in lipid and carbohydrate metabolism are frequently described as genetic markers which influence obesity and other obesity-related phenotypes. Currently, they are also considered in the context of their potential impact on the functional response of the human body to exercise. One of the most investigated obesity markers is *PPARG*, which is expressed in adipocytes and plays an important role in the formation of fat cells, in lipid metabolism and in the development of type 2 diabetes. Our research team has investigated whether body mass changes observed in physically active participants are modulated by the *PPARG* Pro12Ala (rs1801282) genotype. The results suggest that *PPARG* genotype may modulate training-induced body mass measurement changes: after completion of the aerobic training programme, Pro/Pro homozygotes were characterised by a greater decrease of body fat mass measurements in comparison with 12Ala allele carriers. These results indicate that the *PPARG* 12Ala variant may weaken the aerobic training-induced positive effects on body mass measurements [53]. On the other hand, *PPARG* 12Ala carriers seem to benefit more from

the resistance exercise. Indeed, we have previously shown that *PPARG* 12Ala allele was over-represented in three independent cohorts of strength/power athletes and increased cross-sectional area of muscle fibres [54, 55, 56]. Other interventional studies have shown that the relationship of diet and physical activity with fasting insulin differs between *PPARG* Pro12Ala genotypes. The beneficial additive results of exercise and healthy diet were observed only in homozygotes for the Pro12 allele. Meanwhile, in 12Ala allele carriers the association between diet and exercise was more complicated and the change in fasting insulin level was only attenuated when both exposures of diet and activity were simultaneously elevated [57].

LEP and LEPR genes

Leptin, an adipocyte-derived hormone, plays a key role in regulating appetite by its inhibitory effects on food intake and increases in energy expenditure by stimulating the metabolism and physical activity to maintain energy balance [58]. Leptin signalling is mediated by its specific receptor, a single transmembrane protein which belongs to the class I cytokine receptor family [59]. Leptin acts as an afferent signal in a negative feedback loop by binding to the leptin receptor regulating adipose tissue mass [60].

Several polymorphisms of both genes coding leptin (*LEP*) and the leptin receptor (*LEPR*) have been studied in various populations for their potential association with obesity. These common variants also may modify the effects of regular physical activity on various obesity-related traits such as glucose homeostasis [61]. Among these SNPs, the *LEP* A19G polymorphism (rs2167270) of the untranslated region of exon 1 affects leptin concentration. The genotype GG is connected with significantly lower leptin concentrations in comparison with the genotype AA [62]. In a study performed on 242 European-derived participants, Walsh et al. [63] found that subjects homozygous for the G allele may obtain additional health benefits as a result of expending more energy in vigorous intensity physical activity due to their genetic predispositions than carriers of the A allele.

Variants of *LEPR* have also been reported to influence leptin receptor activity. One of them is *LEPR* A668G (rs1137101), which is located in exon 6, a supposed leptin binding region, and as a result impacts binding capacity of the leptin receptor to leptin [64]. The G allele has been associated with greater muscle volume than participants with the AA genotype and a greater subcutaneous fat volume response to a resistance training programme [63].

ADRB2 and ADRB3 genes

The proteins encoded by the β2 adrenergic receptor (*ADRB2*) and the β3 adrenergic receptor (*ADRB3*) genes belong to the family of beta adrenergic receptors, which mediate catecholamine-induced activation of adenylate cyclase through the action of G proteins. They are located in adipose tissue, and involved in energy homeostasis through the mediation of both lipolysis and the thermogenesis rate. Thus genes encoding these receptors are interesting candidates for explaining part of the genetic predisposition to obesity in humans [65, 66].

ADRB2 is a major lipolytic receptor in adipocytes, and genetic polymorphisms in the gene may reduce lipolysis and predispose to obesity. The most frequent variants resulting in amino acid changes investigated in relation to obesity are at codon 16 (Arg16Gly, rs1042713) and codon 27 (Gln27Glu, rs1042714). The Gly16 allele has been associated with lower receptor density, and hence reduced efficiency, in comparison with the Arg16 allele, which may influence the propensity to higher BMI [66]. A study of overweight men who participated in a 24-month weight loss programme consisting of a low-calorie diet and everyday aerobic exercise showed a higher frequency of the Gly16 allele in men resistant to weight loss and those who regained body weight after successful initial weight loss at 6 months [67]. Numerous studies have also shown that the Glu27 allele may limit *ADRB2* downregulation and thus affect body weight [68]. Corbalan et al. [69] reported that women who were more active during their free time and were carriers of the Glu27 allele had higher body weight compared to non-carriers, suggesting that these women may be more resistant to losing weight.

ADRB3 is the key receptor mediating catecholamine-stimulated thermogenesis in adipose tissue [70]. In humans, low ADRB3 activity could promote obesity through decreased function in adipose tissue. The Trp64Arg (rs4994) variant in codon 64 of the *ADRB3* gene has been associated with a tendency toward excess body weight, insulin resistance, and type 2 diabetes [71, 72]. Many studies have shown increased BMI (average 0.28 kg/m^2) in carriers of the Arg64 allele only among sedentary participants, but not in physically active subjects, where genotypic differences in BMI were not found [73, 74, 75]. Other studies have shown that women with the Arg64 allele who participated in lifestyle intervention combining exercise and a low-calorie diet lost less weight than women without the allele, suggesting that the Arg64 allele is associated with difficulty in losing weight through diet and a training programme [76, 77]. However, Phares et al. [78] found that the Arg64 carriers experienced a great loss of fat mass and trunk fat following 24 weeks of aerobic exercise training compared to non-carriers and demonstrated an opposite allelic response to exercise.

CONCLUSIONS

Obesity is a multifactorial abnormality which has a well-confirmed strong genetic basis but requires environmental influences, i.e. high caloric intake and low physical activity, to be manifested. Numerous studies have shown the role of lifestyle including exercise and dietary factors in weight control [79]. However, the problem lies in defining the genes and polymorphisms related to obesity, and describing the mechanisms by which they exert their effects. In view of the fact that DNA variants do not completely explain the heritability of obesity, more studies with appropriate designs and statistical power should be undertaken using the latest genomic methods in sequencing and genotyping, combined with epigenomics, transcriptomics, proteomics, and metabolomics [14,79]. Based on the literature, we speculate that in the near future, more studies will be focused on identifying

genetic markers of other obesity-related traits, e.g. resistance to stress and pain, increased appetite and nutrient preference, as well as temperament.

Another important question is the role of the gene variants on the characteristics and range of the body's adaptive response to training. It is well known that the adaptive changes in the human body in response to regular physical exercise show great individual variance. Consequently, losing weight and changes in obesity-related traits in response to training programmes may be more effective for some genotypes than others. However, the genetic background of these reactions still remains mostly unknown. One of the major aims of exercise genomics is to finally be able to define molecular markers which by themselves or in combination with other biomarkers would make it possible to predict the benefits from a different exercise programmes (e.g. aerobic, resistance or mixed) or a physically active lifestyle [14]. Understanding the genetic background of physiological processes would have an enormous impact not only on individualization of exercise programmes to make them more efficient and safer, but also on improved recovery, traumatology, medical care, diet, supplementation and many other areas [14]. Recently, some studies have tried to answer these questions, but they still represent only the first steps towards an understanding of the genetic factors that influence obesity-related traits, as well as gene variant x physical activity interactions, so further research is necessary.

Nevertheless, the search for genetic markers of the functional response of the human body to physical activities is very complicated, and obtained results may be contradictory. There could be several reasons for this inconsistency: i) heterogeneity between study populations, ii) differences in daily food intake and nutrient preference, iii) discrepancy in the volume, intensity and frequency of exercises and in methods of measuring physical activity, and iv) relatively small size of the study group, which may not possess sufficient statistical power for meaningful analysis and interpretation. A major challenge in this kind of research is the organization of an experiment incorporating regular physical activity, food intake control, examination of genotype distribution, and measurement of body composition, physiological and biochemical parameters before and after performance of the training programme. As a consequence, the number of people participating in lifestyle interventions lasting a few weeks or even months may be limited, and the results are hard to replicate in independent studies.

The importance of genetic studies in modern sport increases every year. Consequently, it is important to discuss the achievements, hopes and fears associated with the rapid development of molecular biology in sport and medical sciences.

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