Medicinska istraživanja 2025 | DOI: 10.5937/medi0-58230

OPEN ACCESS

Medical Research | Published by Faculty of Medicine University of Belgrade

REVIEW ARTICLE

# Genetic foundation of brown adipose tissue and its role in childhood obesity

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**Submitted:** 15 April 2025

**Revised:** 14 November 2025

**Accepted**: 18 November 2025

**Online First:** 20 November 2025

**Published:** 24 December 2025

Check for updates



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## Summary

Obesity is a chronic complex disease, defined by excessive fat deposits, that may have adverse health consequences. Long-term childhood obesity has been linked to the development of different chronic illnesses and is often accompanied by various psychological and social issues. It typically develops due to complex, subtle biological predispositions, exacerbated by social and environmental factors that promote obesogenic behaviors. Brown adipose tissue (BAT) was initially identified as a thermogenic organ in small rodents and human infants. Although its amount decreases with age, adults retain some metabolically active functional BAT tissue, which can help regulate metabolism and energy expenditure, making it a potential target for obesity treatments. Metabolic stress can lead to the "whitening" of BAT, associated with its dysfunction and the development of inflammation and systemic metabolic disorders. Conversely, the transformation of white adipose tissue (WAT) into thermogenic BAT, a process known as "browning", represents another form of adipose tissue "transdifferentiation". In this complex network, specific genes, such as *UCP1*, *PRDM16*, *PPARG*, *PPARGC1A*, and *EBF2*, were identified. Identification of polymorphic variants within BAT-related genes, as well as the hormonal regulation, neurotransmission, and inflammation associated with BAT, could enhance our understanding of the causes of obesity and facilitate the development of novel treatments. This review summarizes recent studies on the genetic regulation of brown adipose tissue (BAT) differentiation and transdifferentiation, as well as gene variants that may predispose individuals to obesity at an early age. Based on this genetic foundation, we also explore and summarize mechanisms to prevent the "whitening" of BAT and its functional decline.

**Keywords**: obesity, brown adipose tissue, children, gene polymorphism

Cite this article as: Maksimovic N, Perovic D, Perovic V, Dusanovic Pjevic M, Grk M. Genetic foundation of brown adipose tissue and its role in childhood obesity; Medicinska istraživanja 2025;58(4):273-83; DOI: 10.5937/medi0-58230

## INTRODUCTION

Obesity, a chronic complex disease defined by excessive fat deposits that have adverse health consequences, is a worldwide growing concern. In recent decades, the frequency of childhood obesity has significantly increased globally and remains alarmingly high. When obesity begins in childhood, it poses a strong risk of becoming a lifelong condition, along with numerous associated complications such as type 2 diabetes or cardiovascular diseases (1). A common misconception is that only high-income countries face such public health issues; in reality, middle-income countries have some of the highest rates of overweight and obesity. Additionally, the annual increase in the prevalence of these conditions is twice as high in low- and middle-income countries compared to high-income countries (2). According to the World Obesity Federation, Serbia has one of the highest obesity rates in Europe. Approximately 15% of boys and 9.3% of girls are classified as obese, while an additional 20.3% of boys and 17.8% of girls are considered overweight (https://data.worldobesity.org/#RS|1|A|F; accessed February 11, 2025). The current projections are not better either. It is estimated that 30% of obese preschool children will become obese adults. Furthermore, 50% of obese children aged 7 to 12 are likely to remain obese as they grow older, while an alarming 70% of obese adolescents are expected to stay obese for life (3).

Obesity in children is seldom attributed to single-gene abnormalities that arise *de novo* or are inherited from parents. Instead, it typically develops due to complex and often subtle biological predispositions, exacerbated by social and environmental factors that promote obesogenic behaviors. Understanding the intricate relationships between these behaviors and their impact on adiposity and the risk of childhood obesity is of paramount significance. Therefore, the prevention and treatment of childhood obesity can encompass a variety of approaches, including alterations to the built environment and policy changes, as well as behavioral, pharmaceutical, and surgical interventions.

Brown adipose tissue (BAT) was originally identified as a thermogenic organ in small rodents and human infants (4). Recent studies show that, although the amount decreases with age, adult humans retain functional BAT. This tissue is metabolically active and has the potential to regulate systemic metabolism and energy expenditure, making it a promising candidate for new obesity treatments (5). Metabolic stress can lead to the "whitening" of BAT, which is associated with its dysfunction and the development of inflammation and systemic metabolic disorders (6). Conversely, the transformation of white adipose tissue (WAT) into thermogenic brown adipose tissue, a process known as "browning", represents another form of adipose tissue "transdifferentiation". In this complex network, specific genes, such as *UCP1, PRDM16, PPARG, PPARGC1A,* and *EBF2*, were identified (7).

This review summarizes recent studies on the genetic regulation of BAT differentiation and transdifferentiation, as well as gene variants that may predispose individuals to obesity from an early age. Based on this genetic foundation, we also explore and summarize mechanisms to prevent the "whitening" of BAT and its functional decline. Understanding these mechanisms could help develop advanced therapies and prevention strategies for pediatric obesity, potentially resulting in a lasting impact on adult health.

## METHODS

To identify studies on the genetic basis of brown adipose tissue and its association with childhood and adolescent obesity, we searched the PubMed database using the following keywords: brown adipose tissue, gene expression, gene polymorphisms, childhood obesity, and adolescent obesity. We considered only articles published in English within the last 15 years.

## BAT ORIGINS AND FUNCTION

There are at least three types of adipose cells: white, brown, and beige. Each type has distinct developmental origins and expresses specific "signature" genes that differentiate it from the others. Apparent anatomical differences exist in lipid droplet localization, lipid droplet size, mitochondrial number, and physiological role. Although endocrine function is consistent, WAT cells primarily serve as energy storage, whereas BAT cells play an important role in thermogenesis. **Figure 1** illustrates the main characteristics and differences between the three types of adipose tissue.

In the 1960s, researchers identified significant amounts of BAT in newborns, with the earliest clear description dating back to the early 20th century. The mitochondrial uncoupling protein 1 (UCP1), associated with BAT, was isolated from human adipose tissue, leading to the development of antibodies that facilitated further exploration of this tissue in adults. This protein was found to be the key regulator of proton conductance in brown fat mitochondria. Interest in brown fat surged in the late 2000s following two key discoveries: that brown adipocytes originate from myogenic precursors in skeletal muscle and that a third type of adipocyte, brite (or beige) fat cells, exist and express UCP1 alongside some markers of brown adipocytes. Recent studies confirm that BAT is present and functional in adult humans (8), supporting findings from the 1980s. Fludeoxyglucose F18, a positron-emitting radiotracer used in positron emission tomography (PET) imaging, reveals that BAT is stimulated by cold and insulin. Still, its activity decreases with age and is lower in obese individuals than in lean individu-

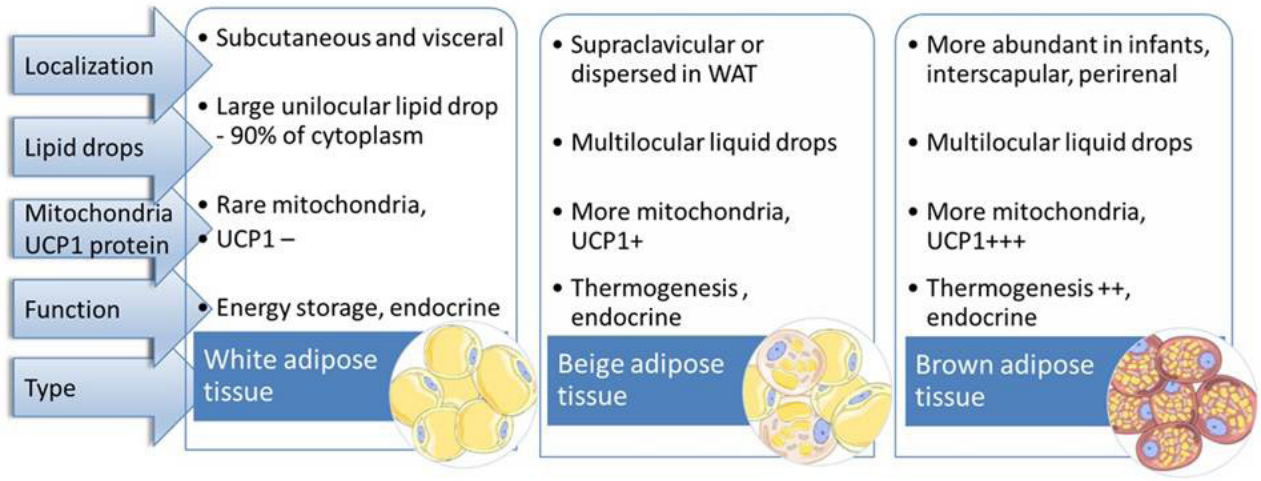


**Figure 1.** Main characteristics of different types of adipose tissue. Adapted from Servier Medical Art (https://smart.servier.com), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).
UCP1: uncoupling protein 1

als, showing an inverse relationship with body mass index (BMI) (9).

Adaptive thermogenesis is an effective strategy for heat production in the BAT of humans and other placental mammals that converts chemically stored energy from fatty acids and glucose to generate heat independently of muscle activity, a process known as non-shivering thermogenesis. This mechanism is particularly important for human infants, as it helps them maintain a high inner body temperature (10). Beige adipose tissue, also known as induced BAT (iBAT), has a different developmental origin but can also produce heat when stimulated. This process relies on the UCP1 protein, which becomes abundant in this tissue. Multilocular lipid stores and the high mitochondrial content in brown adipocytes support thermogenesis.

Additionally, the extensive vascular and nerve supply to this tissue plays a crucial role, particularly through catecholamines released from sympathetic nerve terminals. Sympathetic signaling increases during cold exposure, activating β-adrenergic receptors to enhance thermogenesis in brown adipose tissue. Chronic cold exposure, therefore, could lead to expansion of BAT. Thyroid hormones are also important endocrine inputs for metabolic regulation of this tissue (11). BAT supports cardiometabolic health since it was independently associated with decreased probabilities of type 2 diabetes, dyslipidemia, coronary artery disease, cerebrovascular disease, congestive heart failure, and hypertension. It may help lessen the negative impacts of obesity by regulating triglyceride, high-density lipoprotein, and blood glucose levels (12).

## MOLECULAR SIGNATURE AND GENETICS OF BAT

The molecular basis of the phenotypic differences between white and brown adipose cells has been an open question for some time. Classic brown adipocytes originate from multipotent progenitor cells in somatic mesoderm that express engrailed 1 (*En1*), paired box protein 3 (*Pax3*), *Pax7*, and myogenic factor 5 (*Myf5*) (13). A transcriptional cascade during later embryogenesis induces the development of brown adipocytes from preadipocytes. It is considered that Early B-cell factor 2 (EBF2) is an essential transcriptional regulator during this process (14), and the critical step is the recruitment of the transcription factor PPARγ (Peroxisome proliferator-activated receptor gamma). PPARγ is a key regulator of adipogenesis across all types of fat cells, along with various other DNA-binding factors and co-regulators. For instance, CCAAT/enhancer-binding proteins (C/EBP)-α and -β activate PPARγ expression, regulating adipose differentiation and influencing Ucp1 expression.

Furthermore, Pparα, strongly expressed in BAT, regulates the expression of many thermogenic genes, including Pgc1α and Prdm16. PPARγ coactivator 1α (PGC1α) promotes mitochondrial biogenesis, resulting in the unusually high density of mitochondria in brown and beige adipose tissue. Some other proteins, such as forkhead box C2 protein (FOXC2), can trigger certain aspects of the brown fat phenotype. Adipocyte precursor cells undergoing brite adipogenesis in WAT are thought to share many transcriptional programs with developing brown adipocytes. However, beige adipocytes are located in white fat depots and are considered to be genetically more related to white fat cells with which they share a common precursor, as opposed to brown fat cells, which share an origin with muscle cells (5). When there is no browning stimulation, the transcription factors zinc finger protein 423 (ZFP423) and transducin-like enhancer of split 3 (TLE3), which are enriched in WAT, inhibit EBF2 to suppress a brown fat-like transcriptional program. Other transcriptional coregulators could prevent browning by repressing PGC1-α and disrupting its interaction with PPARγ. On the other hand, overexpression of PGC1-α

and PPARγ induces browning of human mature white adipocytes (15).

## BAT- RELATED GENE VARIANTS AND OBESITY IN CHILDREN

Obesity is a complex disease influenced by both genetic and environmental factors. The heritability of obesity ranges from 40% to 70% (16), underscoring the importance of identifying obesity-related genes for effective treatment (16). The most discussed foundation behind anti-obesity BAT potential is high metabolic activity and oxidative metabolism that drive uncoupled thermogenesis (17). Given the key role of UCP1 in this process, the gene encoding this protein was a logical candidate for examining the association of its polymorphic variants with obesity. The A3826G single-nucleotide polymorphism (SNP) in the upstream region of the *UCP1* gene, specifically the A allele, has attracted significant attention because it is associated with elevated UCP1 expression (18). According to studies, young Japanese males and females with the A allele have lower BMIs and higher energy expenditures (19). In Turkish children, the GG genotype of this polymorphism appears to contribute to the onset of childhood obesity (20). A thorough analysis of the literature, however, shows that the A3826G polymorphism has no consistent effects on human obesity, raising the possibility that previously reported connections are merely accidental (21). Also, no genome-wide association studies (GWAS) on obesity have identified the *UCP1* gene as a candidate; instead, the sole correlation is with physical activity (22). Nevertheless, it was shown that loss of UCP1 expression in subcutaneous adipose tissue could predict obesity from an early age (23), and numerous variants were found in transcriptional regulators of UCP1 expression, such as *PRDM16*, *CTBP2*, *PPARG*, *and PPARGC1A*.

### *PRDM16* gene variants

In the search for key determinants of brown fat cells, PRDM16 was identified as a transcription factor that is significantly more highly expressed in brown fat than in white fat (23). The T-to-C alteration in the 5'-flanking region of the PRDM16 gene, rs12409277, could affect transcriptional activity (24). In the adolescent cohort, Maksimovic et al. did not find an independent association of this SNP with BMI. Still, they revealed that carriers of the CT genotype at rs12409277, in combination with the GG genotype at rs1561589, had significantly lower levels of total cholesterol and LDL cholesterol than all other genotype groups (25). Another polymorphism, rs2236518 (G/T) in the 3′UTR of exon 17, was associated with obesity only among young Chinese males. Subjects who carried the TT genotype had a BMI 3.65% higher than individuals with the GG genotype (26).

### *CTBP2* gene variants

Recent research demonstrated that C-terminal binding protein 2 (CtBP2), a transcriptional corepressor encoded by the *CTBP2* gene, plays a critical role in the pathogenesis of obesity and the metabolic imbalance linked to the condition. Inactivation of CtBP2 leads to obesity, and its overexpression has the opposite effect. It was shown that this protein could "sense" the nutritional status and repress liver glucose and lipid metabolism (27). It also engages PPARα, a key transcription factor for fatty acid oxidation, to diminish its activity. This interaction is intensified when CtBP2 binds to malonyl-CoA, a metabolic intermediate that rises in obese tissues and is known to inhibit fatty acid oxidation by blocking carnitine palmitoyltransferase. This metabolic system, regulated by CtBP2, offers a new perspective on how cells achieve homeostasis by coordinating metabolic processes, and disrupting CtBP2 could serve as a crucial trigger in the development of obesity (28). Recently, Giuranna et al. found five rare variants in *CTBP2* that were exclusively detected in children and adolescents with severe obesity, further emphasizing the importance of this gene in obesity pathogenesis (29).

### *PPARGC1A* gene variants

Peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) plays a key role in mitochondrial biogenesis and oxidative metabolism, gluconeogenesis, insulin sensitivity, and β-oxidation in the liver, as well as in thermogenesis in brown adipose tissue (30). Based on this knowledge, it has been suggested that variants in *the PPARGC1A* gene, encoding PGC-1α, may contribute to the onset of obesity. Within the *PPARGC1A* gene, the most frequently analyzed polymorphism is Gly482Ser (rs8192678). It has been shown that carriers of the Ser (A) variant have a reduced protein expression by 60% in comparison to the carriers of the wild-type Gly (G) variant (31). In the adult population, the association of this polymorphism with increased risk of developing type 2 diabetes mellitus, excess weight, and metabolic syndrome has been well recognized (30). However, few studies have investigated this association in children and adolescents. In the study by Vidovic et al. (32), which examined the correlation between the rs8192678 polymorphism and fasting blood glucose levels, lipid profile, and BMI in the Serbian adolescent population, there was no association between rs8192678 and BMI. In overweight and obese children, LDL-C levels were higher in carriers of the GG genotype than in carriers of the A allele. Brito et al. conducted a study in healthy children and adolescents from the Danish and Estonian populations, and their results did not show a correlation between BMI and the rs8192678 polymorphism in either study group (33). Conversely, in a study of 730 Portuguese children aged

7-12 years, an association between allele A and increased BMI was observed; however, the result was marginally significant (34). The significance of Gly482Ser in children and adolescent populations is still not clear.

### *PPARG* gene variants

PPARγ is a transcription factor belonging to the family of nuclear hormone receptors and plays an important role in adipose tissue differentiation, lipid metabolism, and the regulation of insulin resistance and blood glucose levels (35). Interaction of PPARγ with PRDM16 promotes expression of the UCP1 and other genes specific for BAT and beige adipose tissue. On the other hand, by binding to the Transducin-like enhancer protein 3, PPARγ can have the opposite effect, suppressing the expression of genes specific to brown and beige adipose tissue and stimulating the expression of genes specific to WAT (36). One common polymorphic variant in the *PPARG* gene is the silent C1431T polymorphism (rs3856806) in exon 6. This polymorphic variant is associated with lower body mass index and a favorable lipid profile (37). Even though this polymorphic variant is associated with a better metabolic state, results from different studies remain contradictory. Vidovic et al. did not find a statistically significant association of rs3856806 with BMI (38). This finding aligns with the research conducted by Leon-Mimila et al. (39) and Kim et al. (37). However, in their study of overweight and obese adolescents, they observed that carriers of the CT or TT genotype had lower mean levels of HDL-C compared to those with the CC genotype, although this difference was close to significance. Muntean et al. investigated the contribution of PPARG gene polymorphisms (Pro12Ala rs1801282, His447His rs3856806, and Pro115Gln rs1800571) on the anthropometric and metabolic parameters in a population of normoponderal, overweight, and obese Romanian children. They found no significant differences in allele or genotype distributions among the groups, nor any notable associations with demographic factors or laboratory parameters, including glucose, cholesterol, triglycerides, liver enzymes, and total protein (40).

### *FTO - IRX3* gene variants

Although *FTO* (fat mass and obesity-associated) was the first obesity risk gene identified through GWASs (41), the underlying mechanism remains unknown. A recent systematic review suggests that the polymorphism rs9939609 in FTO (along with rs17782313 in *MC4R*, discussed later) may be linked to overweight and obesity in children and adolescents (42). Some studies indicate that its target, the *IRX3* gene, is likely responsible for preventing white fat browning. Disruption of *IRX3* in animal models inhibits Ucp1 transcriptional activity and reduces uncoupled oxygen consumption. Conversely, overexpression of *IRX3* promoted Ucp1 expression and thermogenesis, reducing fat mass. Additionally, significant enrichment of rare heterozygous missense/frameshift *IRX3* variants was observed in obese subjects (32), providing new evidence that this gene plays an important role in the browning process and human obesity.

## VARIANTS IN GENES INVOLVED IN BAT HORMONAL REGULATION AND NEUROTRANSMISSION

Neurohormonal pathways play a significant role in the pathophysiology of childhood obesity. Adipose tissue is under the control of various humoral, paracrine, or autocrine signaling molecules. Although WAT has been identified as an endocrine organ, little is known about how BAT interacts with other tissues by releasing both protein and non-protein components. Two well-known hormonal regulators of BAT are thyroid and adrenal hormones, and BAT can also secrete the T3 hormone itself (13).

### *DIO2* gene polymorphisms

Thyroid hormones significantly influence BAT. Type II deiodinase (DIO2) provides triiodothyronine (T3) to the nucleus by deiodinating the prohormone thyroxine, facilitating thyroid hormone signaling and enhancing adaptive thermogenesis in BAT and the brain. Recent studies have focused on one SNP in *the DIO2* gene, which is prevalent in human populations at 12%-36%, making it one of the most extensively studied polymorphisms. This common variant, rs225014 (Thr92Ala-*DIO2*), is associated with a broad range of clinical conditions like type 2 diabetes, hypertension, and obesity (43). Compared with euthyroid noncarriers (Thr/Thr), euthyroid and hypothyroid individuals who are Ala92-DIO2 carriers exhibited higher BMI and fasting plasma glucose levels (44). Ota et al. studied the Japanese population of obese children and found that the homozygous Ala/Ala allele of the DIO2 gene significantly increases the risk of pediatric obesity (45).

### β-adrenergic receptor (AR) gene variants

Activating BAT through sympathetic stimulation can help alleviate obesity and related metabolic issues. Norepinephrine, released from sympathetic nerve endings, activates β3-adrenoceptors in mice and β2 in humans and initiates a series of intracellular processes that ultimately lead to the activation of UCP-1 (46). A recent study investigated the role of genetic variants of the β-adrenergic receptor (AR) genes and their relationship with BAT activity in adult humans (47). Their findings indicate that a well-known functional SNP in the *ADRB2* gene (rs1042713, also known as Arg16Gly) is significantly

linked to BAT activity in adults of East Asian descent. This research provides evidence for a genetic predisposition to BAT activity in human adults and supports the idea that β2-AR is crucial for regulating BAT thermogenesis. In a cohort of Brazilian obese/overweight children and adolescents, the Glu16Glu variant of this SNP was linked to better response to physical exercise programs, lower triglyceride levels, and better triglyceride-glucose index (48). Additionally, pharmacogenetic studies suggest that *ADRB2* genotypes are related to how individuals respond to β2-AR agonists or antagonists (49).

### *MC4R* and *FGF21* gene variants

Interestingly, sympathetic BAT inputs could be regulated by the melanocortin 4 receptor, MC4R, and the gene encoding this protein is linked to the most common form of monogenic severe childhood-onset obesity (MIM #618406) (50, 51). As previously mentioned, rs17782313 in the *MC4R* showed a strong association with obesity risk and all components of metabolic syndrome. Another SNP, rs489693, exhibits a consistent recessive effect in severe antipsychotic-induced weight gain (52). The secretion of another autocrine and paracrine molecule, Fibroblast growth factor 21 (FGF21), that enhances glucose uptake and thermogenesis, is linked to induced browning of white adipocytes. The effect of FGF21 is attributed to elevated PGC-1α levels, which, in turn, lead to UCP1 expression (53). Genetic investigations in humans have associated some SNPs within and near the *FGF21* gene with preferences for carbohydrates, proteins, fats, and alcohol (54).

### Serotonin-related gene variants

Food intake and energy expenditure are also regulated by various neurotransmitters and neuropeptides that play roles in energy metabolism. A recent RNA sequencing study of human WAT and BAT preadipocytes confirmed differential gene expression in BAT, including *UCP1*, *DIO2*, *ADRB1*, and *PRDM16*. Notably, the most significant finding was the expression of the *SLC6A4* gene, which encodes the serotonin (5-HT) transporter (SERT). This highlights the importance of serotonin metabolism in brown adipocytes. The authors demonstrated that serotonin inhibits mitochondrial uncoupling by reducing UCP1 expression via activation of the 5-HT2B receptor (55). Several GWAS have identified genetic links between obesity and the serotonergic system. In addition to the *SLC6A4* gene, other genes related to 5-HT receptors or enzymes - including *HTR1B*, *HTR2A*, *HTR2B*, *TPH1*, and *TPH2*- have been particularly noted in the adolescent population (56). Overall, these findings suggest that 5-HT plays a role in regulating BAT thermogenesis. Furthermore, they indicate that individuals with lower levels of 5-HT activity may be more susceptible to β3-adrenergic medications (57).

### *BDNF* gene variants

Based on results from animal models, it was suggested that brain-derived neurotrophic factor (BDNF) mediates BAT thermogenesis. Selective disruption of *BDNF* expression from promoter 1 results in severe obesity in animal models and reduced expression of Pgc1α and Ucp1 (58). BDNF is a member of the neurotrophin family and is crucial for neuronal survival and differentiation, synaptic plasticity, and brain connectivity. It also plays a significant role in regulating food intake, managing weight, maintaining glucose balance, overseeing energy balance, and controlling blood pressure and lipid levels (59). Several SNPs in the *BDNF* gene sequence have been studied, with the most commonly analysed being rs6265 (c.196G>A, Val66Met). This particular SNP results in a change from valine to methionine at the 66th amino acid position in the prodomain of the BDNF protein. The presence of the Met allele causes the abnormal intracellular trafficking and packaging of pro-BDNF and impacts the secretion of mature peptides (60). Results regarding the association of the rs6265 polymorphism with BMI, fasting glucose levels, and lipid status in adolescents have been contradictory. In the study by Vidovic et al., conducted on Serbian adolescents, a significant association between the Val66Met polymorphism and fasting blood glucose levels was observed. In contrast, associations with BMI and lipid status were not (61). A meta-analysis by Daher et al. on the association between the Val66Met polymorphism and obesity risk found that the Val/Val genotype is associated with an increased risk of obesity among adults but a reduced risk among adolescents. One possible explanation for these contradictory results is the complex mechanism of BDNF expression regulation (62).

## VARIANTS IN GENES INVOLVED IN BAT INFLAMMATION

BAT is generally more resistant to inflammation than WAT. However, recent studies indicate that enhanced inflammation impairs the ability of brown adipocytes to expend energy and to take up glucose, and plays a major role in their whitening, which contributes to metabolic diseases linked with obesity (63). Numerous immune cells infiltrate BAT and communicate with one another via signaling molecules, such as interleukin 6 (IL-6). Genetic variants in various innate immunity genes encoding cytokines, cytokine receptors, complement system genes, proinflammatory signaling genes, or suppressors of cytokine signaling correlate with obesity. Some of the research included children (64). Recent research has highlighted the connection between BAT, inflammation, and the role of omega-3 polyunsaturated fatty acids (PUFAs) in modulating adipose tissue function (65). Omega-3 fatty acids, particularly eicosapentaenoic acid (EPA)

and docosahexaenoic acid (DHA), have been shown to exert significant effects on WAT function and browning. Chronic low-grade inflammation, a characteristic of obesity, is influenced by omega-3 PUFA activity, which can mediate metabolic and pro-inflammatory pathways. Studies indicate that omega-3 supplementation reduces WAT inflammation by down-regulating immune-related gene expression and decreasing pro-inflammatory cytokines such as TNF-α and MCP-1 (66).

A key emerging factor in the interplay between BAT, inflammation, and metabolic regulation is Galectin-3 (Gal-3). Gal-3, a β-galactoside-binding lectin, plays a critical role in immune modulation and tissue homeostasis (67). Gal-3 knockout mice fed a high-fat diet exhibited increased body weight, visceral adiposity, hyperglycemia, and insulin resistance. These mice also showed elevated pro-inflammatory immune responses, including higher numbers of Th1 and natural killer T (NKT) cells, CD11c+CD11b+ macrophages, and increased NLRP3 inflammasome activation, NF-κB activity, and IL-1β production in pancreatic and peritoneal macrophages (68). Moreover, Gal-3 deficiency was associated with increased adipose tissue inflammation, characterized by higher macrophage infiltration and elevated levels of IL-6 and TNF-α. A high-fat diet further exacerbated this inflammatory state by downregulating adiponectin and PPAR-γ expression, which are essential for maintaining insulin sensitivity (69).

A recent study has explored the genetic variations in the *LGALS3* gene, particularly the rs4644 polymorphism, which has been associated with metabolic traits such as obesity, lipid metabolism, and insulin resistance. By regulating immune cell interactions within adipose depots, Gal-3 may either facilitate or hinder the browning process. Research among adolescents demonstrated that the CC genotype of the rs4644 polymorphism is associated with higher body mass index (BMI) and increased triglyceride levels, particularly in female participants (70). These findings suggest that genetic factors may influence Gal-3 expression levels, which in turn affect adipose tissue function and inflammation. In the context of BAT, Gal-3 may modulate thermogenic activity and affect beige adipocyte differentiation (71). Additionally, Gal-3 has been associated with adipose tissue fibrosis, which could affect BAT function and its ability to counteract metabolic inflammation (72).

Mature brown fat cells are terminally differentiated. Nevertheless, BAT also contains stromal vascular fraction (SVF), which includes preadipocytes. By using collagenase digestion, SVF can be separated from mature adipocytes, allowing preadipocytes to differentiate into mature brown adipocytes for applications such as genetic intervention or pharmacological stimulation.

## THERAPEUTIC POTENTIAL OF BAT

The causes of obesity in childhood and adolescence are complex, making prevention and management rather challenging. The first-line treatment for childhood obesity typically focuses on lifestyle changes, including a calorie-reduced diet, increased physical activity, and behavioral therapy (73). In recent years, BAT has emerged as an appealing target for obesity treatment. Activating BAT has potential benefits, including anti-obesity effects and lowering cholesterol and glucose levels, which could be leveraged therapeutically. However, most experimental studies of this type have been conducted in animal models. Substantial issues still need to be addressed before considering BAT activation or the "browning" of WAT as viable intervention strategies for humans, particularly children.

Activation of BAT can be achieved through exposure to cold, exercise, dietary changes, and some small-molecule treatments. **Figure 2** summarizes some of the potential therapeutics that act through activation of BAT and/or browning of WAT.

Recent studies have highlighted the potential role of small molecules in certain fruits and vegetables in modulating WAT browning and activating BAT. Long-term consumption of compounds such as capsaicin, its esters, ephedrine, and green tea can directly activate brown fat (74). However, more research is needed to understand better how small molecules can be safely and effectively used to increase BAT activity in children.

The pharmacological treatment for obesity in children and adolescents includes the application of GLP-1 receptor agonists, specifically Liraglutide and Semaglutide. Liraglutide is approved by both the FDA (Food and Drug Administration) and the EMA (European Medicines Agency), while Semaglutide is approved by the FDA. Both medications reduce hunger by acting on central nervous system targets and by slowing gastric emptying. Additionally, these medications can induce weight loss, decrease the risk of adverse cardiovascular events, and improve type II diabetes (75). They can be used to treat obesity in children aged 12 to 17 years (weight > 60 kg and BMI> 30 kg/m2 / ≥ 95th percentile) (73). Preclinical data have been encouraging. It has been shown that Liraglutide stimulates mitochondrial respiration and biogenesis in human adipocytes, potentially through UCP-1-mediated adipocyte browning (76). However, there is limited clinical evidence regarding the contribution of GLP-1 receptor agonists (GLP-1RAs) to BAT activation.

## CONCLUSION

Brown adipose tissue has attracted significant attention for its unique thermogenic properties and its role in metabolic health. With renewed interest in BAT's role in obesity, researchers are exploring its activation as a potential

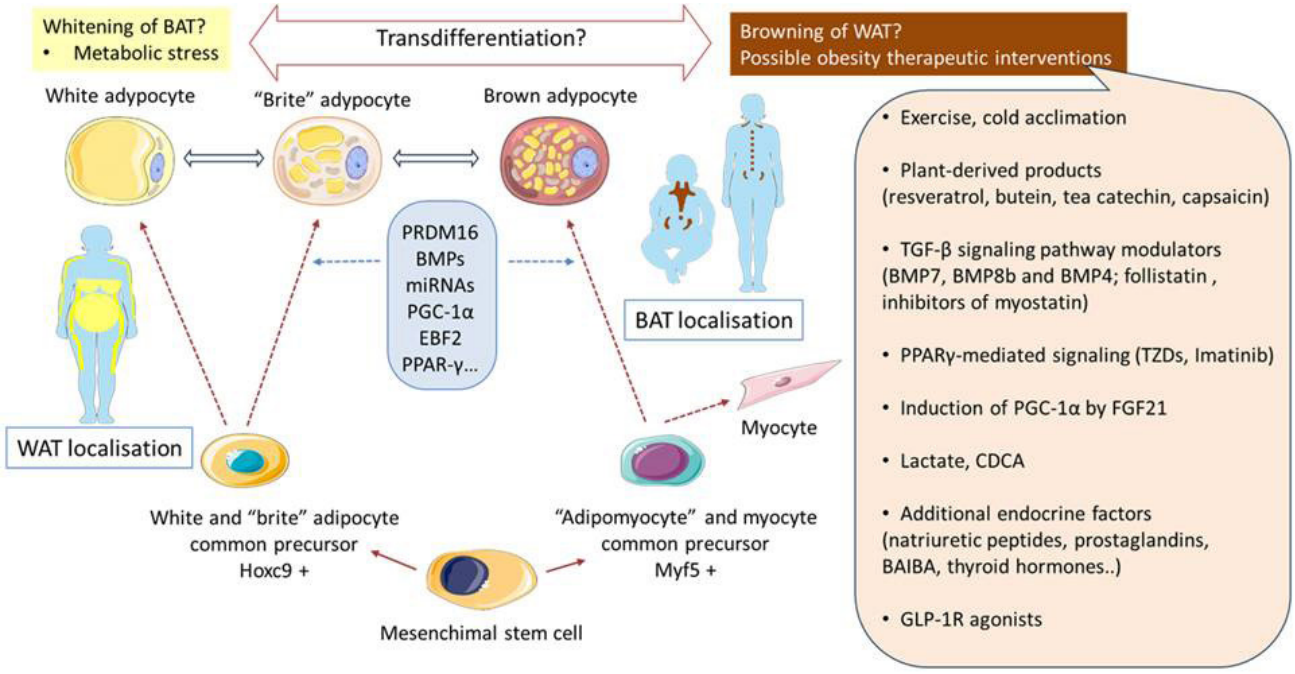


**Figure 2.** Origin and routes of differentiation/ transdifferentiation of adipose tissue with reference to possible therapeutic options. Adapted from Servier Medical Art (https://smart.servier.com), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).
BAT, brown adipose tissue; BAIBA: β-aminoisobutyric acid; BMPs: bone morphogenic proteins; CDCA: chenodeoxycholic acid; EBF2: Early B-cell factor 2; FGF21: Fibroblast growth factor 21; GLP-1R: Glucagon-like peptide-1 receptor; miRNAs: micro RNAs; Myf5: Myogenic Factor 5; Pgc-1α: Pparγ coactivator 1α; PRDM16: PR domain containing 16; PPARγ: Peroxisome-proliferator activated receptor gamma; TGF-β: Transforming growth factor beta TZDs: Thiazolidinediones; WAT: white adipose tissue

treatment. Although BAT can detect and influence energy metabolism, at this stage, maximizing tissue activity is challenging and may not be suitable for all individuals and patient populations. It has not been proven yet that BAT activation can effectively induce weight loss and protect against the adverse effects of obesity. Further research in this field is needed to better understand its function, the influence of gene variants crucial to its differentiation and activity on weight gain, and its potential therapeutic effects.

**Acknowledgments:** The authors would like to acknowledge all the researchers and participants of the JUSAD (Yugoslav study of atherosclerosis precursors in schoolchildren in Serbia) study.

**Funding information:** the presented article was part of the project funded by the Ministry of Science, Technological Development, and Innovation of the Republic of Serbia, grant no. 451-03-66/2024-03/200110.

**Conflicts of interest:** The authors have no conflicts of interest to report.

**Author Contributions:** Conceptualization, N.M. and D.P.; Writing - Original draft preparation, N.M., D.P., V.P., M.G., and M.D.P.; Writing - Review and Editing, N.M. and D.P.

**Ethical approval:** N/A

**Informed consent:** N/A

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# GENETIČKA OSNOVA MRKOG MASNOG TKIVA I NJEGOVA ULOGA U DEČIJOJ GOJAZNOSTI

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**Sažetak**

Gojaznost je kompleksna hronična bolest, definisana prisustvom prekomernih masnih naslaga, koje mogu imati štetne posledice po zdravlje. Dugotrajna gojaznost u detinjstvu je povezana sa razvojem različitih hroničnih bolesti i često je praćena psihološkim i socijalnim problemima. Obično nastaje na terenu složene i suptilne biološke predispozicije, pogoršane faktorima društvene i životne sredine koji promovišu ponašanje koje vodi u gojaznost. Mrko masno tkivo (*brown adipose tissue*, BAT) je prvobitno identifikovano kao termogeni organ kod malih glodara i novorođenčadi. Iako se smanjuje sa godinama, odrasle osobe zadržavaju određenu količinu metabolički aktivnog funkcionalnog BAT-a koje ima potencijal da reguliše sistemski metabolizam i potrošnju energije, što ga čini potencijalnim kandidatom za lečenje gojaznosti. Metabolički stres može dovesti do toga da BAT „pobeli", što je povezano sa njegovom disfunkcijom i razvojem zapaljenja i sistemskih metaboličkih poremećaja. Suprotno tome, transformacija belog masnog tkiva (*white adipose tissue*, WAT) u termogeno mrko masno tkivo, predstavlja još jedan oblik „transdiferencijacije" masnog tkiva. U ovoj složenoj mreži izdvojeni su specifični geni poput *UCP1, PRDM16, PPARG, PPARGC1A i EBF2*. Identifikacija polimorfnih varijanti u genima vezanim za BAT, kao i hormonska regulacija, neurotransmisija i inflamacija povezana sa mrkim adipocitima, mogla bi poboljšati naše razumevanje uzroka gojaznosti i olakšati razvoj novih tretmana. Ovaj revijalni rad rezimira nedavne studije o genskoj regulaciji diferencijacije i transdiferencijacije BAT-a, kao i varijante gena uključenih u ove procese koji mogu predisponirati pojedince na gojaznost od ranog uzrasta. Takođe, istražujemo i sumiramo mehanizme koji mogu sprečiti transformaciju mrkog u belo masno tkivo i gubitak njegove funkcije.

**Ključne reči:** gojaznost, mrko masno tkivo, deca, polimorfizmi gena

**Primljen:** 15.04.2025. I **Revidiran:** 14.11.2025. I **Prihvaćen:** 18.11.2025. I **Online First:** 20.11.2025. I **Objavljen:** 24.12.2025.

**Medicinska istraživanja 2025**