

MC4R: A Genetic Key to Metabolic and Cardiovascular Disorders

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ABSTRACT

The melanocortin-4 receptor (MC4R) is a critical regulator of energy homeostasis, lipid metabolism, and cardiovascular risk factors. First cloned in 1993, MC4R's role in appetite regulation was confirmed through animal studies, and its genetic mutations were later identified as major contributors to monogenic obesity. This review synthesizes current research on MC4R's genetic variations and their implications for obesity, metabolic disorders, and cardiovascular health. A systematic literature review was conducted, adhering to PRISMA guidelines, with data extracted from PubMed, Scopus, Web of Science, and Google Scholar. Studies from 1992 to 2025 focusing on MC4R mutations, their effects on obesity, type 2 diabetes, dyslipidemia, and hypertension, as well as their contribution to cardiovascular risk were included. Recent insights highlight rare MC4R variants, such as p.Ser36Thr and p.Ala175Thr which are associated with severe obesity, and novel structural variants, e.g., p.Ser85Gly, which destabilize signaling pathways. Loss-of-function MC4R variants cause hyperphagia and early-onset obesity, whereas gain-of-function variants enhance satiety, providing protection against obesity. MC4R dysfunction also impacts glucose homeostasis and lipid metabolism, thereby increasing the risk of type 2 diabetes, dyslipidemia, and hypertension. Additionally, alterations in MC4R increase cardiovascular risk via pathways involving energy imbalance, sympathetic activation, and endothelial dysfunction. This review highlights the genetic underpinnings of MC4R in metabolic and cardiovascular diseases and underscores the need for developing targeted therapeutic strategies.

KEYWORDS melanocortin-4 receptor, metabolic disorders, cardiovascular disorders, obesity, MC4R mutations

INTRODUCTION

The melanocortin 4 receptor (MC4R) is a protein encoded by the MC4R gene in humans. It is a type of G-protein-coupled receptor (GPCR) that binds to α -melanocyte stimulating hormone (α -MSH). This receptor plays a crucial role in

regulating energy homeostasis, feeding behavior, metabolism, and body weight (1). The MC4R was first cloned in 1993 using degenerate PCR, although its function was initially unclear. Subsequent research suggested its potential role in regulating energy homeostasis, a hypothesis that was con-

firmed in 1997 by seminal studies in mice which demonstrated the receptor's influence on appetite and energy balance. By 1998, human genetic studies identified mutations in the MC4R gene as a cause of monogenic obesity (2).

The MC4R gene, located on chromosome 18q21.3, encodes a 332-amino acid protein that serves as a key regulator of energy homeostasis, appetite, food intake, and body weight at the hypothalamic level. As a prototypical GPCR and one of the five members of the melanocortin receptor family, MC4R plays a pivotal role in maintaining energy balance (3, 4). It is activated by melanocortin's peptide hormones derived from the proteolytic cleavage of the proopiomelanocortin (POMC) protein (5). The receptor is widely expressed in the brain, including regions such as the cortex, thalamus, hypothalamus, brainstem, and spinal cord. In addition to its critical role in energy metabolism, MC4R influences blood pressure, heart rate, and erectile function (6). Dysregulation of MC4R signaling contributes to dyslipidemia, characterized by elevated triglycerides and low-density lipoprotein (LDL) cholesterol (7). It also exacerbates insulin resistance and promotes the release of adipokines, such as resistin, which are implicated in inflammation and endothelial dysfunction, thereby increasing cardiovascular risk

(8). These diverse functions underscore MC4R's importance as a target for treating metabolic and cardiovascular disorders.

This review will delve into the critical role of MC4R in metabolic and cardiovascular disorders, highlighting its genetic influence on energy balance, obesity, and related comorbidities. It will also explore the potential effect of targeting MC4R pathways for therapeutic interventions to mitigate these risks. By identifying populations with genetic variations in MC4R and developing precision-based treatment strategies, healthcare professionals and researchers can advance the development of improved metabolic and cardiovascular health outcomes globally.

METHODS

The stepwise approach depicted in Figure 1 illustrates the rigorous assessment of full-text articles, ensuring the inclusion of studies directly addressing the MC4R-metabolic and cardiovascular link.

MC4R: STRUCTURE AND FUNCTION

MC4R is a rhodopsin-like class A peptide GPCR and belongs to the melanocortin receptor family, which comprises five receptor subtypes (MC1R to MC5R) (9). MC4R encodes a protein called

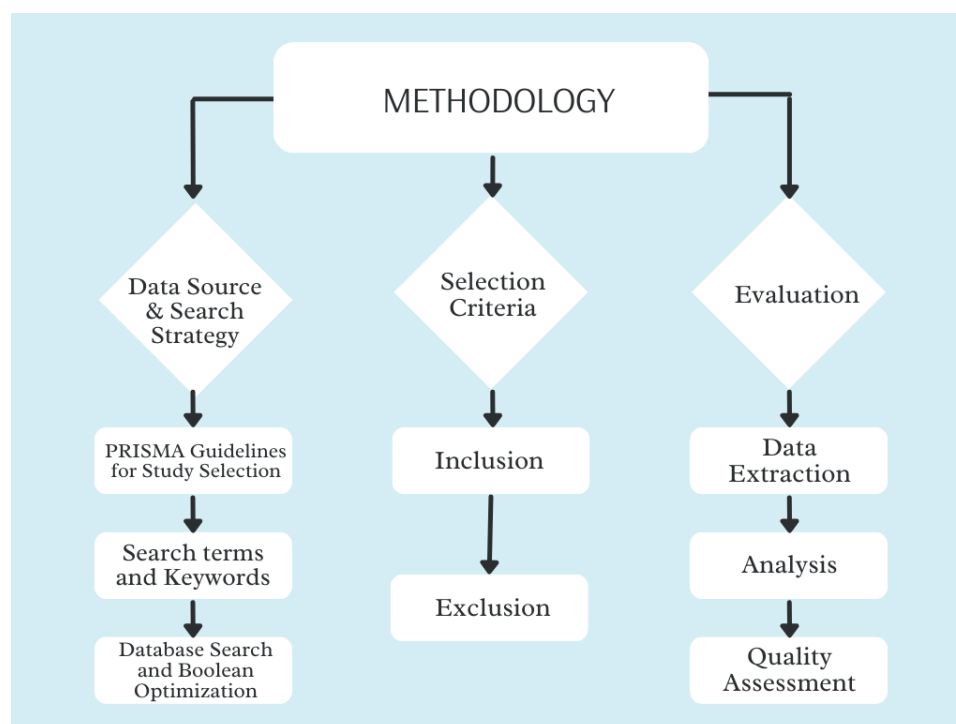


Figure 1. Methodology

melanocortin 4 receptor, primarily expressed in the hypothalamus, where it regulates appetite and satiety. It functions as a GPCR that binds to α -MSH (10). Activation of MC4R by its natural agonists, α -MSH or β -MSH, induces appetite-suppressing effects (11).

MC4R primarily couples with the stimulatory G-protein transducer (Gs) to activate adenylyl cyclase (AC), resulting in the production of intracellular cyclic adenosine monophosphate (cAMP) and subsequent activation of protein kinase A (PKA). In addition to Gs-mediated signaling, MC4R can engage other G-protein-dependent cytosolic transducers, including Gi and Gq/11 (12). Furthermore, MC4R also interacts with G-protein-independent transducers such as β -arrestin and the Kir7.1 ion channel (13).

The MC4R is a crucial component of the leptin-melanocortin molecular axis, which governs hunger, satiety, and energy balance. Brain-derived hormones, such as α -MSH and agouti-related peptide (AgRP), regulate this axis. When α -MSH, an agonist, binds to MC4R, it activates signaling pathways in the brain that promote satiety and reduce food intake. In contrast, AgRP, an inverse agonist, blocks this effect, thereby stimulating appetite (14). MC4R is essential for regulating food intake, energy homeostasis, and body weight (15). Mutations in the MC4R gene can significantly affect metabolic outcomes. Loss-of-function mutations in MC4R or deficiencies in POMC, the precursor of melanocortin receptor agonists, are linked to hyperphagia and severe early-onset obesity (16). Conversely, gain-of-function mutations enhance satiety, decrease food intake, and contribute to lower body weight (17).

MC4R SIGNALING PATHWAYS AND DOWNSTREAM EFFECTS.

MC4R, a GPCR, primarily signals through the stimulatory G-protein (Gs), leading to the activation of AC and the subsequent intracellular production of cAMP. The elevated cAMP levels activate PKA, which phosphorylates various target proteins to elicit diverse cellular responses (14). Functionally, MC4R is crucial for maintaining energy balance by regulating both food intake and energy expenditure, as its activation suppresses appetite and promotes energy utilization (2). Beyond its metabolic roles, MC4R activation also

affects cardiovascular function by contributing to the regulation of blood pressure and heart rate (18).

Guo et al., highlighted that MC4R plays a critical role in maintaining physiological balance across multiple systems. In energy homeostasis, MC4R regulates both food intake and energy expenditure, with its activation reducing appetite and promoting energy utilization, making it essential for body weight management (19). In the cardiovascular system, MC4R activation contributes to the regulation of blood pressure and heart rate, supporting cardiovascular stability (18). Its influence also extends to glucose and lipid metabolism, where MC4R signaling optimizes glucose utilization and lipid storage, thereby reducing the risk of metabolic disorders (20). Zhao et al. emphasized MC4R's role in the nervous system, including regulation of pain perception, anxiety, stress responses, and sensory processing (21). This wide-ranging functionality underscores MC4R's significance in maintaining systemic health and overall homeostasis.

ROLE OF MC4R IN THE CENTRAL NERVOUS SYSTEM AND PERIPHERAL TISSUES

MC4R is predominantly expressed in the hypothalamus, particularly in the paraventricular nucleus (PVN), the dorsal motor nucleus of the vagus (DMV), and the intermediolateral nucleus of the spinal cord (IML), where it plays a central role in regulating energy balance and feeding behavior. Additionally, MC4R participates in central nervous system (CNS) functions, including stress modulation, neuropathic pain regulation, and cardiovascular homeostasis (22). Beyond the CNS, MC4R expression extends to adipose tissue, influencing lipid metabolism and energy expenditure (23). It is also present in intestinal L cells, where it contributes to the secretion of incretin hormones that regulate glucose homeostasis (24). Furthermore, MC4R is expressed in peripheral nerves and muscles, supporting organ homeostasis and tissue regeneration (22).

RECENT FINDINGS ON MC4R VARIANTS

MC4R (melanocortin-4 receptor) variants are known to play a significant role in obesity and metabolic disorders. The identification and functional characterization of rare and pathogenic MC4R variants across diverse populations provide

valuable insights into the genetic basis of severe obesity. In a Brazilian cohort, several rare missense mutations, including p.Ser36Thr, p.Val103Ile, p.Ala175Thr, and p.Ile251Leu2, were significantly associated with elevated body weight and BMI, highlighting the impact of these genetic alterations on obesity susceptibility (25). Further investigations in Qatar uncovered two novel variants, c.253A>G (p.Ser85Gly) and c.802T>C (p.Tyr268His), in individuals with morbid obesity. Functional analyses revealed that these variants destabilized MC4R protein structure, impairing its signaling pathways and underscoring its critical role in energy regulation and weight control (26). In Singapore, studies on Asian children with severe early-onset obesity identified the variants c.127C>A (p.Gln43Lys) and c.272T>G (p.Met91Arg), both of which exhibited defective cAMP signaling, a key pathway in energy homeostasis. These mutations disrupt MC4R function, leading to disturbances in metabolism (27). Collectively, these studies highlight the global prevalence and functional importance of MC4R variants in the etiology of severe obesity, providing a foundation for targeted therapeutic strategies and precision medicine approaches.

Table 1 presents recent studies conducted in different populations, identifying specific MC4R variants and their functional implications in obesity, emphasizing structural, signaling, and phenotypic associations.

MC4R AND METABOLIC DISORDERS

Obesity and weight regulation

Obesity affects over 30% of adults and children worldwide, representing a critical public health

challenge. It results from an imbalance in energy homeostasis and is associated with various comorbidities, including type 2 diabetes, cardiovascular diseases, certain cancers, infertility, and psychological conditions such as depression (28). While an obesogenic environment and sedentary lifestyle are major contributors, genetic factors also play a significant role in regulating body weight (29).

Although most cases of obesity have a polygenic basis, a subset of individuals develop monogenic obesity, often caused by pathogenic variants in genes that influence the leptin-melanocortin pathway, an essential hypothalamic system for appetite regulation (30). Among these, mutations in the MC4R gene, a G-protein-coupled receptor, are the most common cause of monogenic obesity, significantly impairing energy balance and appetite control (2). This highlights the interplay between genetic predisposition and environmental factors in obesity and underscores the need for precision-targeted therapeutic strategies.

Genetic insights into MC4R mutations

Mutations in the MC4R gene, typically inherited in an autosomal dominant manner, are the most frequent monogenic cause of obesity, with over 200 variants identified (25). These mutations occur in 2-3% of tested populations and account for approximately 6% of obesity cases, establishing them as the leading cause of non-syndromic monogenic obesity (29).

Heterozygous loss-of-function mutations are the most prevalent, whereas homozygous or compound heterozygous mutations are less common (31, 32). Individuals with inactivating

Table 1. Recent studies on MC4R variants and their findings

Study	Location/ population	MC4R Variants Identified	Findings
Identification of a rare and potential Pathogenic MC4R variant in a Brazilian Patient with adulthood-onset severe obesity	Brazil	p.Ser36Thr, p.Val103Ile, p.Ala175Thr, p.Ile251Leu	Variants associated with higher body weight and BMI (25)
Functional characterization of novel MC4R variants	Qatar	c.253A>G p.Ser85Gly, c.802T>C p.Tyr268His	Variants destabilize MC4R structure and affect signalling pathways (26)
MC4R variants in Asian children with severe obesity	Singapore	c.127C>A p.Gln43Lys, c.272T>G p.Met91Arg	Variants show defective cAMP signalling activity (27)

mutations-of-function mutations often exhibit early-onset obesity, hyperphagia, hyperinsulinemia, increased linear growth, and elevated bone mineral density (33). Prevalence rates vary among ethnic groups, with lower frequencies (less than 1%) observed in Asian populations and estimates of less than 2% in large Caucasian European and American cohorts (34).

Conversely, gain-of-function mutations in MC4R exert protective effects. These variants are associated with lower body mass index (BMI) and reduced risks of obesity, type 2 diabetes, and coronary artery disease. Their protective effects are attributed to variants favoring β -arrestin-biased signaling, which enhances mitogen-activated protein kinase pathway activation. This unique signaling mechanism represents a promising therapeutic target for weight management and treatment of obesity-related cardiometabolic conditions (17).

While monogenic obesity arises from single-gene mutations such as those in MC4R, polygenic obesity results from the combined influence of multiple common genetic variants and is considerably more prevalent (35). Understanding these distinct genetic contributions provides potential avenues for precision medicine approaches in obesity management.

Table 2 summarizes the types of MC4R genetic mutations, their prevalence, and associated phenotypic consequences, distinguishing between loss-of-function, gain-of-function, and compound heterozygous variants with relevance to obesity and metabolic health.

Associated gene mutations

Mutations in the MC4R gene are the primary genetic cause of monogenic obesity, encompassing various mutation types, including missense, nonsense, and frameshift mutations, which result in partial or complete loss of MC4R function (25). These alterations impair the receptor's capacity to regulate energy balance, thereby contributing to severe obesity. Common variants near the MC4R gene, such as rs17782313 and rs17700633, have been extensively studied and are linked to increased susceptibility to obesity and insulin resistance, further highlighting the gene's role in metabolic regulation (36). In addition to these common variants, rare MC4R mutations, including p.Ser36Thr, p.Val103Ile, p.Ala175Thr, and p.Ile251Leu, have been identified in individuals with severe obesity, underscoring the significant contribution of rare genetic alterations to extreme phenotypes (25). Collectively, these findings emphasize the critical role of MC4R in energy homeostasis and its importance as a target for understanding and managing obesity.

Type 2 diabetes and insulin resistance

The MC4R plays a crucial role in regulating energy balance and insulin secretion. It is essential for controlling appetite and maintaining metabolic homeostasis, and its dysfunction can result in various metabolic abnormalities (20). According to Morgan and colleagues, MC4R signaling in the hypothalamus influences glucose homeostasis and insulin sensitivity (37). Research has demonstrated a link between MC4R dysfunction and an increased risk of type 2 diabetes.

Table 2. Genetic variants in MC4R and their implications for obesity

Mutation type	Prevalence	Phenotypic effects	References
Loss-of-function (LoF)	2–3% in tested populations; ~6% of obesity cases	Early-onset obesity - Hyperphagia - Hyperinsulinemia - Increased linear growth - Elevated bone mineral density	(29, 31, 32, 33)
Homozygous/compound heterozygous LoF	Rare	More severe phenotypes than heterozygous mutations	(31)
Gain-of-function (GoF)	Rare, protective	- Lower body mass index - Reduced risk of obesity - Reduced risk of type 2 diabetes - Reduced risk of coronary artery disease	(17)

Insulin resistance, hyperglycemia, and other metabolic disturbances are frequently observed in individuals with MC4R alterations (38). A 2015 study by Morgan et al. highlighted that MC4R signaling in the lateral hypothalamus is critical for regulating glucose tolerance and sympathetic activity, both of which are essential for maintaining metabolic health (37).

Dyslipidemia and hypertension

Dyslipidemia and hypertension are key cardiovascular risk factors that often coexist. Dyslipidemia is characterized by abnormal blood lipid levels, including elevated total cholesterol, triglycerides, and LDL cholesterol, along with reduced high-density lipoprotein (HDL) cholesterol levels (39). Hypertension, commonly known as high blood pressure, damages blood capillaries and promotes atherosclerosis, significantly increasing the risk of heart disease and stroke (40). Recent studies have highlighted that MC4R signaling in the CNS plays a critical role in regulating energy balance, food intake, and fat storage. The MC4R exerts significant influence on lipid metabolism by coordinating both central and peripheral mechanisms. Through various signaling pathways, MC4R modulates lipid metabolism in white adipose tissue (WAT) and brown adipose tissue. This dual regulatory function underscores its importance in maintaining energy homeostasis and preventing metabolic dysregulation (41).

MC4R and lipid metabolism

The MC4R plays an essential role in lipid metabolism by coordinating energy balance and fat distribution through both central and peripheral mechanisms (42). Within the CNS, MC4R is a key component of the hypothalamic leptin-melanocortin signaling pathway, which regulates appetite and energy expenditure (43). By modulating sympathetic nervous system (SNS) activity, MC4R affects adipose tissue metabolism. Specifically, it promotes lipolysis in WAT via β -adrenergic receptor activation, facilitating fat breakdown. Concurrently, MC4R activation enhances thermogenesis in brown adipose tissue, increasing energy expenditure by converting stored lipids into heat (41). Emerging studies also suggest that MC4R may directly interact with lipid-metabolizing enzymes, further emphasizing its role in

maintaining lipid homeostasis. These functions highlight MC4R's potential as a therapeutic target for obesity and related metabolic disorders (44).

Hypertensive effects of MC4R dysfunction in obesity

Dysfunction of the MC4R in obesity can exacerbate the development of hypertension. Obesity is a major risk factor for hypertension, and disruptions in MC4R can further exacerbate this risk by affecting energy balance and metabolic regulation (45). According to Metzger et al., impaired MC4R signaling is associated with elevated blood pressure and a higher likelihood of cardiovascular complications (42).

Potential mechanisms linking MC4R to cardiovascular risk factors

MC4R is involved in several physiological processes that contribute to cardiovascular risk factors. According to Kleinau and co-authors, MC4R plays a pivotal role in regulating energy homeostasis, influencing both food intake and energy expenditure, which are essential for maintaining metabolic balance. Disruption of MC4R function, often through gene mutations, can lead to obesity, a condition that substantially increases the risk of cardiovascular diseases (46). Koochakpoor and colleagues highlighted that obesity associated with MC4R dysfunction is also closely linked to alterations in lipid metabolism, including dyslipidemia, a well-established risk factor for cardiovascular conditions (44). Furthermore, MC4R dysfunction exacerbates the inflammatory response and endothelial dysfunction, both key contributors to the progression of cardiovascular diseases (47). According to da Silva et al., activation of the SNS due to MC4R disruption further amplifies these risks by increasing blood pressure and heart rate, thereby placing additional strain on the cardiovascular system (48). Collectively, these processes highlight the integral role of MC4R not only in metabolic regulation but also in the pathophysiology of obesity-related cardiovascular diseases.

MC4R AND CARDIOVASCULAR DISEASE

Genetic alterations in MC4R are strongly linked to obesity and metabolic syndrome, both of which are major contributors to cardiovascular disease (CVD) (2). Investigating the connection

between MC4R and CVD may facilitate the development of targeted therapeutic strategies. MC4R is located in the hypothalamus, where it plays a pivotal role in controlling appetite and satiety. As a component of the melanocortin system, it helps monitor and respond to over-nutrition, thereby regulating metabolism to prevent obesity. When MC4R malfunctions, it can result in hyperphagia (excessive eating) and early-onset obesity, both of which elevate the risk of cardiovascular diseases (49). Recent research has identified MC4R variants, such as rs17782313, as contributors to an increased risk of obesity and metabolic dysfunction. Carriers of these variants often exhibit higher BMI, increased waist circumference, and elevated blood glucose levels, all recognized risk factors for cardiovascular diseases (50). Cardio-metabolic syndrome comprises a group of conditions that increase the risk of heart disease, stroke, and diabetes. MC4R deficiency disrupts glucose homeostasis, thereby raising the likelihood of insulin resistance and type 2 diabetes, primarily because MC4R is essential for maintaining energy balance and metabolic regulation (51).

Impact on insulin sensitivity

A 2024 study by Guo and co-authors explored the impact of hypothalamic MC4R knockout specifically in POMC neurons on insulin sensitivity. The findings revealed that MC4R deficiency impairs insulin sensitivity by modulating Kir2.1 activity. Deletion of MC4R in POMC neurons resulted in increased food intake, reduced energy expenditure, and disrupted systemic glucose regulation (19). Mechanistically, the study by Cui et al. identified a direct interaction between MC4R and Kir2.1, and that silencing Kir2.1 reversed the negative effects of MC4R ablation on energy expenditure and glucose homeostasis (52). Another study by Ni et al. examined the role of MC4R in pancreatic islets and its regulation of insulin secretion via the cAMP and β -arrestin-1 pathways (20). That research demonstrated that MC4R activation by the agonist NDP- α -MSH significantly increased the expression of prohormone convertase 1/3 (PC1/3), a key factor in insulin secretion. Conversely, MC4R inhibition with the antagonist AgRP reduced PC1/3 expression. These results indicate that MC4R regulates PC1/3 expression through the cAMP and β -arrestin-1 pathways,

thereby modulating insulin secretion (20).

MC4R in hypertension

Da Silva and fellow authors in 2019 highlighted the role of the brain MC4R in modulating SNS activity. Dysregulated MC4R signaling increases SNS activity, promoting hypertension, a major contributor to CVD. The study emphasized that MC4R activation is critical not only for obesity-induced hypertension but also for other forms of hypertension associated with heightened SNS activity (48). Sull and co-authors investigated the association of MC4R variants with diabetes and CVD in Korean men and women. The study found that individuals with the TC/CC genotype of the MC4R rs17782313 SNP exhibited a higher risk of diabetes and cardiovascular disease, independent of obesity, suggesting a direct role of MC4R in cardiovascular regulation (7). Collectively, these studies underscore the importance of MC4R in blood pressure regulation and highlight its potential as a therapeutic target for hypertension and cardiovascular disease.

MC4R and atherosclerosis

Mutations in the MC4R gene, known to cause monogenic obesity, can trigger systemic inflammation, a major contributor to endothelial dysfunction and the development of atherosclerosis (2). The MC4R pathway plays an essential role in managing energy balance, glucose levels, and lipid metabolism. Impaired MC4R signaling disrupts these metabolic processes, leading to increased inflammation and a heightened risk of atherosclerosis (53). Altered lipid metabolism caused by MC4R variants can significantly accelerate plaque formation. Research by Adamska-Patruno and co-authors indicates that these mutations are associated with reduced visceral fat accumulation but cause a relatively greater increase in postprandial carbohydrate utilization. This metabolic shift can elevate circulating lipid concentrations, promoting the development of atherosclerotic plaques and increasing the risk of coronary artery disease (54).

THERAPEUTIC IMPLICATIONS OF MC4R

Recent advancements have focused on developing both agonists and antagonists targeting MC4R to address metabolic disorders. Among

these, setmelanotide, an MC4R agonist, has demonstrated significant therapeutic potential for severe obesity associated with genetic defects in the leptin-melanocortin pathway. Clinical studies have shown its effectiveness, with a phase 3 trial reporting substantial weight loss and reduced hunger levels in individuals with POMC- or LEPR deficiency-related obesity. The treatment was generally well tolerated, with no new safety concerns identified (55).

In addition to obesity management, MC4R modulation may confer cardiovascular benefits. Research indicates that MC4R agonists can improve metabolic profiles, potentially aiding in the prevention and management of cardiovascular diseases (1). However, translating these promising preclinical findings into clinical practice remains challenging.

Emerging technologies, such as CRISPR-Cas9, offer potential for correcting alterations in MC4R, paving the way for precision medicine (56). Furthermore, combining MC4R agonists with other agents, such as GLP-1 receptor agonists, has shown synergistic effects, enhancing weight loss and improving metabolic outcomes (57). These developments underscore the therapeutic potential of MC4R-targeted interventions in addressing obesity and its related comorbidities.

CONCLUSIONS

In conclusion, the MC4R gene is a central regulator in the pathogenesis of metabolic and cardiovascular disorders, particularly through its role in obesity. Mutations in the MC4R gene, which include missense, nonsense, and frameshift alterations, often impair receptor function, leading to severe obesity. Common variants, such as rs17782313 and rs17700633, are associated with a higher risk of obesity and insulin resistance, while rare mutations, including p.Ser36Thr, p.Val103Ile, and p.Ala175Thr, contribute to more extreme obesity phenotypes. These genetic alterations disrupt the receptor's normal regulation of energy balance, emphasizing the critical role of MC4R in both weight management and metabolic health.

Moreover, alterations in MC4R influence cardiovascular function in addition to contributing to obesity. As obesity is a well-established risk factor for CVDs, MC4R dysfunction can exacerbate

conditions such as hypertension, dyslipidemia, and atherosclerosis, thereby increasing overall cardiovascular risk. The intersection of obesity and cardiovascular health associated with MC4R variants highlights the need to better understand its genetic and physiological mechanisms.

Future research on MC4R may facilitate the development of innovative therapeutic strategies, including targeted interventions to restore MC4R function or modulate its signaling pathways. Such approaches would be particularly beneficial for individuals with genetic predispositions to obesity and cardiovascular diseases, paving the way for more personalized treatments. Overall, MC4R remains a key genetic factor at the forefront of understanding the complex relationship between metabolic and cardiovascular disorders, highlighting its potential as a therapeutic target to address these interconnected health challenges.

Future perspectives

Therapeutic strategies targeting MC4R hold significant promise for addressing obesity-related cardiovascular risks. The development of selective MC4R agonists, gene therapy approaches to correct pathogenic variants, and combination therapies with other metabolic regulators, such as GLP-1 receptor agonists, may enhance efficacy in weight reduction and cardiometabolic risk management. Moreover, advances in precision medicine and CRISPR-Cas9 technologies could enable personalized interventions tailored to specific MC4R genotypes, allowing clinicians to optimize treatment for individuals at highest risk of metabolic and cardiovascular complications. Collectively, these emerging approaches highlight a new era in translating genetic insights into effective therapies for obesity-associated cardiovascular disease.

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CONFLICT OF INTEREST

The authors report no potential conflict of interest.

AUTHOR CONTRIBUTION

J.P.J.: conceptualization, methodology design, sample collection, laboratory work (biochemical and molecular analyses), data acquisition, statistical analysis, and manuscript drafting; S.K.B.: supervision, critical review of study design, interpretation of molecular data, guidance in laboratory methodologies, and manuscript revision for important intellectual content; N.M.: validation of biochemical assay procedures, clinical correlation of metabolic findings, and critical inputs in manuscript development; K.R.K.: administrative support, regulatory approvals, and institutional coordination for ethical clearance and research execution; N.M.: clinical insight into endocrine aspects, interpretation of hormonal and metabolic data, and contribution to discussion and conclusions; VMG, SJP, SM, ST: assistance in sample processing, ELISA/RT-PCR experimentation, data entry, and preliminary statistical evaluation; HPH, RR, PK, TA: support in genetic data analysis and visualization, referencing, and manuscript formatting; DRD: conceptual supervision, molecular diagnostics consultation (MC4R expression), manuscript review, critical editing, and final approval of the version to be published.

DATA AVAILABILITY STATEMENT

This review synthesizes and critically analyzes data from previously published studies; all data are publicly available through the cited literature, ensuring transparency and reproducibility of the findings discussed.

INSTITUTIONAL REVIEW BOARD STATEMENT

This review article does not report on new experimental research involving humans or animals; therefore, ethics approval was not required.

INFORMED CONSENT STATEMENT

This review article does not include research involving human participants; therefore, informed consent was not required.

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