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Rare Neurogenetic Signatures in Brain Circuits: A Novel Axis in Metabolic Syndrome Susceptibility

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ABSTRACT

Metabolic syndrome (MetS), a cluster of conditions including central obesity, insulin resistance, dyslipidemia, and hypertension imposes a large burden on global health, yet substantial phenotypic variability persists across individuals with similar lifestyle exposures. While common polygenic risk variants and environmental factors are well characterized, the contribution of rare, high-impact genetic variants affecting neurocircuitry that governs energy homeostasis has not been systematically explored. In this article, we review evidence implicating rare functional variants in central neuroregulatory genes (notably MC4R, BDNF/TrkB, and LEPR) in human and animal models of obesity, hyperphagia, insulin resistance, and other metabolic perturbations. We show these genes are expressed in key brain regions including hypothalamic nuclei and reward pathways that integrate peripheral metabolic signals to regulate appetite, energy expenditure, and glucose/lipid homeostasis. Based on this evidence, we propose the "Gene-Brain-Metabolic Axis" framework, in which rare neurogenetic variants disrupt central neural circuits, increasing susceptibility to MetS independent of environmental risk. Recognizing this axis may (1) explain a portion of unexplained inter-individual heterogeneity in MetS, (2) inform precision-screening strategies, and (3) suggest novel central nervous system targeted therapies (e.g., receptor agonists or neurotrophic modulation). We highlight key gaps and call for integrated studies combining genetics, neuroimaging, metabolic phenotyping, and behavioral assessment.

Keywords

Metabolic syndrome, Neurogenetics, Hypothalamus, Melanocortin-4 receptor, BDNF, Leptin receptor, Energy homeostasis, Brain-metabolic axis, Rare variants.

Introduction

Metabolic syndrome (MetS) has emerged as a major global health challenge, linking central adiposity with insulin resistance, dyslipidemia, hypertension, and increased risk of type 2 diabetes and cardiovascular disease [1,2]. Conventional models attribute MetS to lifestyle factors (sedentary behavior, caloric excess) combined with the cumulative effect of common polygenic risk variants [3-5]. However, even among individuals with comparable environmental exposures, metabolic trajectories often diverge substantially some remain metabolically healthy, while others rapidly develop full-blown MetS. This unexplained heterogeneity suggests additional biological layers of susceptibility beyond common genetic risk and lifestyle.

Rare, high-impact variants affecting central neuroregulatory pathways represent a promising, yet under-explored, dimension. Key brain structure including the hypothalamus (arcuate nucleus, paraventricular nucleus, ventromedial hypothalamus), brainstem, and mesolimbic reward circuits integrate hormonal and nutrient signals (leptin, insulin, ghrelin) to control feeding, energy expenditure, and metabolic homeostasis [3,6,7]. Disruption of these circuits could predispose individuals to obesity, insulin resistance, and other MetS components, independent of diet or

physical activity.

Genes such as MC4R, BDNF, and LEPR encode central regulators of these neural circuits. Loss-of-function (LoF) mutations in MC4R are the most frequent identifiable cause of monogenic obesity, affecting satiety signaling, basal energy expenditure, and glucose homeostasis [4,7]. BDNF and its receptor TrkB mediate neuronal plasticity and hypothalamic development; rare variants alter synaptic connectivity in energy-regulating circuits, contributing to hyperphagia and metabolic disturbances [3,8]. Similarly, LEPR mutations impair leptin signaling, promoting early-onset obesity, insulin resistance, and dyslipidemia [9,10].

We propose the **"Gene-Brain-Metabolic Axis"**, a conceptual framework in which rare neurogenetic variants disrupt central neural circuits, leading to systemic metabolic dysregulation. This review synthesizes existing evidence for these neurogenetic contributions, proposes a model linking brain circuits to metabolic syndrome, and outlines potential research and therapeutic implications.

Neurogenetic Influences on Metabolism

MC4R (Melanocortin-4 Receptor)

MC4R is expressed primarily in hypothalamic nuclei controlling satiety and energy expenditure. Rare LoF MC4R mutations are a leading monogenic cause of severe early-onset obesity, characterized by hyperphagia, increased visceral adiposity, insulin resistance, and impaired energy balance [4,7].

Animal models demonstrate that Mc4r-null mice develop obesity even under controlled food intake due to reduced basal energy expenditure, highlighting the central neurogenic mechanism [5]. Human studies similarly show that carriers of heterozygous LoF MC4R variants exhibit elevated BMI, visceral fat, and impaired glucose homeostasis [4]. These findings support the role of MC4R in predisposing to MetS via hypothalamic circuit dysfunction.

BDNF (Brain-Derived Neurotrophic Factor)

BDNF regulates neuronal development, synaptic plasticity, and hypothalamic function. Rare variants in BDNF or TrkB are associated with hyperphagia, severe obesity, and metabolic disturbances [3,8]. Preclinical studies indicate that hypothalamic BDNF therapy in MC4R-deficient mice prevents obesity, hyperinsulinemia, and other metabolic syndrome features [3]. The human BDNF Val66Met polymorphism has been linked to obesity and altered energy balance, though associations vary across populations [3,11]. BDNF interacts with melanocortin pathways, highlighting a mechanistic bridge between neurotrophic signaling and energy homeostasis.

Leptin/Leptin Receptor (LEP/LEPR)

Leptin signaling via LEPR is essential for CNS-mediated regulation of appetite, energy expenditure, and glucose metabolism [9,10]. Rare LEPR variants cause early-onset obesity, hyperphagia, insulin resistance, and dyslipidemia. Heterozygous variants in the leptin-melanocortin pathway amplify weight gain in children, demonstrating a direct neurogenic contribution to metabolic syndrome [9,12]. Together, these findings suggest that LEPR variants, like MC4R and BDNF, contribute to MetS via disruption of hypothalamic and reward circuits.

Conceptual Framework: Gene-Brain-Metabolic Axis

We propose the **Gene-Brain-Metabolic Axis**, in which rare neurogenetic variants influence systemic metabolism through central neural pathways. The axis consists of three key components:

1. **Genetic Input:** Rare or damaging variants in neuroregulatory genes (MC4R, BDNF, LEPR).
2. **Neural Processing:** Dysregulation of hypothalamic, mesolimbic, and cortical circuits controlling appetite, reward, and energy expenditure.

Systemic Output: Altered feeding behavior, visceral adiposity, insulin resistance, and reduced energy expenditure, manifesting as MetS.

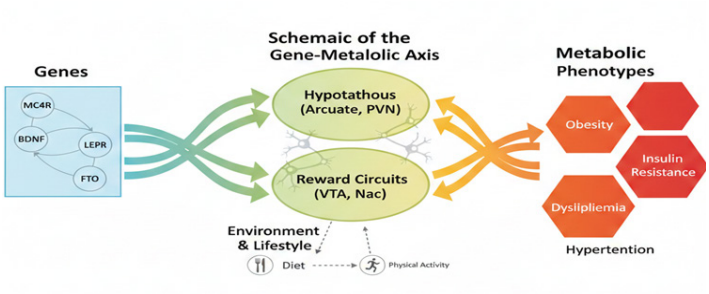

Figure 1: *Schematic of the Gene-Brain-Metabolic Axis.* This framework helps explain phenotypic variability in MetS beyond lifestyle and polygenic risk factors and integrates human genetics with central neural control.

Implications

The conceptualization of the Gene-Brain-Metabolic Axis provides multiple avenues for translational, clinical, and research impact. By explicitly linking rare neurogenetic variants to central neural circuits regulating energy homeostasis, this framework informs strategies for precision medicine, novel therapeutic interventions, integrated research approaches, and ethical practice in metabolic syndrome management.

Precision Screening

Identification of rare, high impact neurogenetic variants offers an unprecedented opportunity to stratify individuals according to inherent risk for metabolic dysregulation. Conventional risk assessment models rely heavily on polygenic risk scores, lifestyle factors, and standard anthropometric measures, which often fail to capture the subset of individuals who develop MetS despite healthy behavior profiles. By incorporating rare variant screening for example, MC4R LoF mutations, BDNF haploinsufficiency, or LEPR functional deficits clinicians could detect at-risk individuals prior to overt clinical manifestation [4,10,13].

The translational potential is significant: early detection could prompt tailored interventions, including dietary guidance,

structured exercise programs, pharmacologic modulation of appetite or energy expenditure, and close monitoring of glycemic and lipid parameters. Furthermore, integrating rare variant data with polygenic and environmental factors can refine risk prediction models, enhancing the sensitivity and specificity of metabolic syndrome prognostication. Over time, longitudinal studies incorporating these precision metrics could reveal the penetrance and expressivity of rare variants, providing robust evidence for risk-based screening protocols.

Targeted Therapies

The Gene–Brain–Metabolic Axis framework highlights the therapeutic potential of interventions directly targeting CNS pathways disrupted by rare variants. For MC4R-related obesity, central agonists such as Setmelanotide have demonstrated efficacy in restoring satiety signaling, reducing hyperphagia, and improving metabolic outcomes in genetically defined cohorts [3,7,14]. Similarly, neurotrophic modulation of BDNF-TrkB signaling could represent a novel avenue for restoring hypothalamic plasticity and correcting maladaptive feeding circuits.

These precision interventions offer several advantages over conventional systemic therapies. By directly addressing the neurogenic etiology of metabolic dysregulation, central-acting therapies may reduce off-target effects, improve adherence, and produce durable metabolic benefits. Future research could explore combination strategies integrating pharmacologic CNS-targeted agents with behavioral or lifestyle interventions, potentially achieving synergistic effects. Additionally, preclinical models could inform optimal dosing strategies, timing of intervention, and identification of biomarkers for treatment response.

Research Integration

To validate and operationalize the Gene–Brain–Metabolic Axis, a multi-modal research approach is essential. Integrative studies combining high-resolution neuroimaging, functional genomics, metabolomics, and behavioral phenotyping can delineate how rare variants perturb specific neural circuits and downstream systemic metabolism [1,2,15].

For example, structural and functional MRI could quantify alterations in hypothalamic and mesolimbic reward networks in variant carriers. Concurrently, metabolomic profiling could identify early biochemical signatures of energy imbalance, while longitudinal behavioral studies could capture compensatory feeding patterns or altered physical activity. Integration of these datasets through computational modeling and machine learning would allow researchers to predict individual susceptibility, mechanistic pathways, and potential therapeutic targets. Such approaches could also illuminate gene-environment interactions, clarifying why individuals with identical rare variants display variable phenotypic expressivity.

Ethical Considerations

While the clinical and research opportunities are substantial, they are accompanied by significant ethical challenges. Genetic screening for rare neurogenetic variants raises questions about privacy, data security, and potential discrimination in healthcare or employment settings. Counseling protocols must ensure that individuals understand the probabilistic nature of risk conferred by these variants and the limitations of current interventions.

Central nervous system–targeted therapies, particularly those influencing appetite, reward, or satiety, also carry psychosocial implications. Modifying neurocircuitry may affect not only metabolism but also behavior, mood, or cognition, necessitating rigorous preclinical and clinical evaluation of off-target effects. Equitable access to precision screening and targeted therapies must be prioritized to prevent exacerbation of health disparities. Ethical frameworks should therefore integrate principles of beneficence, autonomy, and justice, ensuring responsible translation of neurogenetic insights into clinical practice.

Limitations

Despite the promising insights provided by the Gene–Brain–Metabolic Axis, several important limitations warrant consideration. First, translational gaps exist between preclinical animal models and human physiology; while rodent studies have elucidated mechanistic links between MC4R, BDNF, and LEPR variants and energy homeostasis, differences in brain architecture, metabolism, and compensatory pathways may limit the generalizability of these findings to humans. Second, rare neurogenetic variants inherently affect only a small subset of the population. Although their effect sizes are often large at the individual level, they may not fully account for the broader prevalence or heterogeneity of metabolic syndrome across diverse populations. Third, environmental exposures, lifestyle factors, and epigenetic modifications can modulate the penetrance and expressivity of these variants, complicating the establishment of a direct causal pathway from gene to metabolic phenotype. Finally, current understanding of circuit-level mechanisms remains incomplete. The precise neural circuits through which these genes influence appetite, reward, energy expenditure, and glucose homeostasis are only partially mapped, and the dynamic interactions between different brain regions are not yet fully elucidated. Collectively, these limitations underscore the need for integrative, longitudinal, and multi-modal human studies that combine genomics, neuroimaging, metabolic phenotyping, and behavioral assessment to validate and refine the Gene-Brain-Metabolic Axis framework.

Conclusion

Rare neurogenetic variants in MC4R, BDNF, and LEPR predispose individuals to metabolic syndrome through central dysregulation of brain circuits governing appetite, energy balance, and glucose homeostasis. The Gene-Brain-Metabolic Axis provides a unifying framework connecting genetics, neurobiology, and systemic metabolism. Recognizing this axis can guide precision screening, inform CNS-targeted therapies, and shape future research into metabolic heterogeneity.

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