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Genomics-Metabolomics Integration in Neurometabolic and Rare Neurologic Disorders: Diagnostic Pathways and Clinical Impact

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Abstract This study investigates the integrated application of genomics and metabolomics in the field of neurometabolic and rare neurologic disorders, and systematically elaborates on the core causes of neural metabolic imbalance. It also analyzes the application value and challenges in variant interpretation of high-throughput sequencing technology in genomics for the diagnosis of rare neurologic disorders, as well as the advantages of metabolomic technical platforms such as mass spectrometry and nuclear magnetic resonance, the discovery and validation of disease-related markers, and the application value of metabolic monitoring in efficacy evaluation. The study focuses on the integration strategies for genetic and metabolic data, including the functional correlations among genes, proteins and metabolites, analytical methods such as pathway enrichment, and the construction of clinically applicable multi-omics diagnostic workflows. Combined with three clinical cases of mitochondrial encephalopathy, fatty acid oxidation disorders and lysosomal storage disorders, it verifies the practical efficacy of integrated omics diagnosis. In addition, the study points out that this integration model can significantly shorten the diagnostic time and improve the diagnostic rate, facilitate the accurate stratification of patients and the formulation of individualized treatment plans, and optimize prognosis assessment and long-term disease management. Meanwhile, it also analyzes the current challenges faced by omics integration, such as inadequate data standardization, privacy and ethical issues, and the limitations of artificial intelligence in the application of rare disease research and clinical practice. This study aims to provide a comprehensive theoretical and practical reference for the precise diagnosis and treatment of neurometabolic and rare neurologic disorders.

Keywords Genomics-metabolomics integration; Neurometabolic disorders; Rare neurologic disorders; Disease diagnosis; Metabolic markers

1 Introduction

The normal functioning of the nervous system requires a lot of energy. The stable supply of energy to the brain is crucial for the transmission of information by nerve cells. Mitochondria are the "energy factories" of cells, which can provide energy to nerve cells and also regulate calcium ions. If there are problems with mitochondria or abnormal metabolism of energy substances such as glucose, it may damage cells (Xie et al., 2025b). Many studies have found that in the early stages of some neurological diseases, mitochondrial function is abnormal, indicating that metabolism is related to the occurrence of diseases and may become a target for treatment (Zhang et al., 2025a).

Metabolic studies typically employ two techniques. Many rare neurodevelopmental disorders are related to genetics, and the symptoms of such diseases are often quite similar, such as microcephaly and epilepsy. However, even the same genetic changes may manifest differently in different individuals. High-throughput sequencing can help identify the relevant genes and the causes of the diseases, but it also poses certain difficulties for disease diagnosis (Airoldi et al., 2025; Bakare, 2025). Therefore, we need a comprehensive approach that combines genetics, cellular metabolism, and neural network functions for research.

This study focused on how rare and common genetic variations affect neuro-metabolism and the risk of neurodegenerative diseases. Through metabolomics analysis, changes in metabolic pathways can be observed more directly, helping to identify abnormal metabolic patterns. In the research of rare diseases, the combined analysis of genomics and metabolomics has successfully discovered multiple new pathogenic genes, verified the effects of enzyme or transporter protein variations, and also found biomarkers that are helpful for diagnosis.