metabolic data and genetic data together can help identify lipid metabolism processes related to cognitive ability, track the upstream genes controlling this process, and provide a clearer understanding of the mutual influence between lipid metabolism and amino acid metabolism. Another study detected proteins, metabolites, and inflammatory factors in cerebrospinal fluid, and found that the metabolic levels related to amyloid protein were different. This can help simplify diagnostic indicators. In the research on Fragile X syndrome, metabolic pathway analysis can also assist researchers in identifying clear pathways and potential therapeutic targets from numerous scattered metabolic changes.

After the introduction of artificial intelligence, these analyses have become more efficient. For instance, in the research of multiple sclerosis, using artificial neural networks to analyze blood metabolic data has achieved a very high diagnostic accuracy. In the research of Parkinson's disease, a team developed a model that combines metabolic imaging and clinical indicators, which can help clarify the unique metabolic patterns of this disease and improve the accuracy of early diagnosis (Liu et al., 2025). In the case of Alzheimer's disease, some studies have established a computational platform that integrates multi-omics data and gene metabolic networks to screen therapeutic targets and identify disease characteristics (Yang et al., 2025; Xie et al., 2025a). Applying these methods to rare neuro-metabolic diseases can make variant interpretation and pathway screening more automated and efficient.

5.3 Establishing a clinically applicable multi-omics diagnostic process

Clinically useful genome–metabolome workflows must balance mechanistic depth with feasibility, turnaround time, and interpretability. In rare neurological disease, a practical strategy is to combine WES/WGS with targeted or untargeted metabolomics early in the diagnostic pathway, using genomic data to nominate candidate genes and metabolomics to confirm pathway disruption or to highlight unsuspected metabolic defects. For adult-onset neurometabolic disorders, guidelines already recommend parallel NGS and “deep biochemical phenotyping”; emerging work suggests that untargeted metabolomics can serve as a high-dimensional biochemical screen that both directs further testing and assists in interpreting variants of uncertain significance detected by NGS. Case-based evidence shows that integrated WGS-metabolomics workups in complex pediatric neurogenetic presentations can elucidate composite phenotypes driven by multiple variants and provide pathway-level insights relevant to management.

To make such comprehensive testing a routine procedure, unified sample processing, analysis and reporting steps need to be established. In studies on multi-omics diagnosis of neurodevelopmental disorders and some tumors, some feasible approaches have been used: uniformly collecting samples, simultaneously obtaining multi-omics data, using computational models to identify abnormalities, integrating related pathways, and finally through multidisciplinary discussions, determining the significance of the variations and possible treatment targets (Șerban et al., 2025). Currently, multi-omics data is more suitable for being used in combination, verified through the common involved signaling pathways and candidate markers. The final conclusion still requires comprehensive judgment by experts. With more and more data and the continuous improvement of artificial intelligence models, it is possible in the future to form a standardized gene-pathway-metabolite reporting system, providing more intelligent clinical decision-making assistance for neuro-metabolism and rare neurological diseases.

6 Application Cases of Comprehensive Diagnosis

6.1 Mitochondrial encephalopathy: the interrelationship between metabolomics and genetics

Mitochondrial encephalopathy is a typical example that clearly demonstrates the significant role of metabolic genomics in understanding the impact of genetic changes. Taking MELAS syndrome as an example, researchers analyzed mitochondrial DNA mutations and changes in intracellular metabolites together. They discovered that a metabolite called glutamate showed abnormalities, and its level was closely related to the severity of the genetic mutation. This indicates that glutamate can be used to assess the severity of the disease. Urine analysis also revealed that 36 metabolites in MELAS patients were different from those of healthy individuals, and these changes were mainly related to oxidative imbalance and abnormal fat metabolism. Additionally, some patient indicators (such as FGF21) were significantly elevated, which can serve as an auxiliary method for monitoring