changes in mitochondrial damage. These studies all indicate that in diseases like mitochondrial encephalopathy, combining genetic testing with metabolic indicators can lead to more comprehensive diagnostic results (Zhang et al., 2025b).

6.2 Fatty acid oxidation disorders: association between acylcarnitine profiles and genotypes

Fatty acid oxidation disorders represent another typical case where metabolism is closely linked to genetics. In newborn screening, tandem mass spectrometry is commonly used to detect acylcarnitines in dried blood spots. Different fatty acid oxidation disorders present characteristic profiles, for instance, patients with medium-chain acyl-CoA dehydrogenase deficiency have elevated C8 carnitine, while those with very long-chain acyl-CoA dehydrogenase deficiency show an increase in long-chain acylcarnitines. These metabolic clues can directly guide subsequent genetic testing. Studies in newborn screening cohorts in China and Spain have shown that when the acylcarnitine profile is abnormal, further sequencing of related genes not only enables a clear diagnosis but also establishes the association between genotype and metabolic phenotype (Zhang et al., 2025b; Mayoral et al., 2025).

For example, in primary carnitine deficiency, children carrying a homozygous R254* mutation have significantly lower free carnitine levels than those with compound heterozygous mutations, indicating that the type of mutation directly affects the severity of the metabolism. For multiple acyl-CoA dehydrogenase deficiencies, studies have found that characteristic metabolites may fluctuate over time, so diagnosis requires both genetic testing and multiple metabolic assessments. These experiences demonstrate that in fatty acid oxidation disorders, tandem mass spectrometry provides an efficient initial screening method, while genetic testing is responsible for identifying the cause. The combination of the two can improve diagnostic accuracy and provide a basis for subsequent management.

6.3 Lysosomal storage disorders: multimodal analysis reveals common changes

Lysosomal storage disorders are a group of diseases caused by a single genetic defect. However, the accumulation of substrates triggers a series of secondary changes, such as abnormal autophagy, lipid metabolism disorders, and mitochondrial dysfunction. Recent multimodal studies have begun to systematically depict these downstream effects. For instance, a study simultaneously analyzed the protein and lipid changes in more than twenty types of lysosomal storage disorder mutant cells, revealing that although the pathogenic genes were different, common phenotypes such as autophagy defects and specific lipid elevations were ubiquitous. This provides a new perspective for understanding the disease mechanism and identifying cross-disease treatment targets (Kraus et al., 2025).

Taking Pompe disease as an example, GAA gene mutations not only cause glycogen accumulation but also lead to extensive changes in various metabolites such as sugars, lipids, and amino acids in muscles and body fluids, and different types of patients have different metabolic characteristics. After combining genotype data, these metabolic information helps explain the diversity of clinical manifestations and provides references for the selection of timing for enzyme replacement therapy and efficacy monitoring. Overall, the research on lysosomal storage disorders is shifting from single-gene testing to multimodal integrated analysis. This approach helps shorten the diagnostic cycle, verify the pathogenicity of variations, and discover potential early biomarkers (Yen et al., 2025).

7 Optimization of Diagnostic Procedures and Their Clinical Significance

7.1 Shorten the diagnosis time and increase the diagnosis rate

Many patients with rare neuro-metabolic diseases often spend several years and visit several hospitals before they can be diagnosed. This process is both costly and time-consuming, and sometimes it even delays treatment. If high-throughput genetic testing is adopted at an early stage of the disease, combined with detailed biochemical analysis, the time required for diagnosis can be significantly shortened. For example, for patients with undetermined causes of intellectual disability and metabolic abnormalities, if whole-exome sequencing is used and combined with clinical and biochemical indicators for analysis, the diagnosis rate can reach 68%; while using only genetic testing, the diagnosis rate is only 16%. Studies have pointed out that using whole-exome sequencing as the preferred examination method can eliminate many unnecessary test items, and on average, each patient can save approximately 3,000 euros in costs. In pediatric neuro-metabolic diseases, whole-exome sequencing can help