metabolites. In long-term follow-up, multiple indicator combinations can be constructed to track the disease progression and treatment response with higher temporal resolution. These dynamic metabolic indicators can complement genetic data and comprehensively reflect the effects of genetic background, environment, and treatment factors on cellular metabolism, providing strong support for the research on precise treatment of neurometabolic and rare neurological diseases.

5 Integration Strategy of Genetic and Metabolic Data

5.1 Functional connections among genes, proteins and metabolites

In rare neuro-metabolic diseases, combining genetic data with metabolic data for analysis is intuitive: genetic changes can alter protein functions, thereby affecting the levels of metabolites in the body. Through this correlation, it is possible to determine whether a certain genetic variation truly has an effect. For example, when sequencing reveals suspicious variations in genes related to enzymes, metabolomics can detect an increase or decrease in downstream metabolites, providing more evidence for genetic diagnosis. Studies have shown that in a pair of twins with complex neurodevelopmental problems, whole-genome sequencing identified rare variations in two genes, and at the same time, plasma metabolomics also revealed amino acid metabolism disorders in them. The results of the two methods mutually corroborate, linking genetic variations with clinical symptoms.

Some studies use network analysis to present the relationships between genes, proteins and metabolites graphically. For example, in the animal research of Fragile X syndrome, researchers placed the discovered metabolic changes within the known protein relationship network, clearly showing the impact of the absence of key proteins on processes such as neural signal transmission. In neuromuscular diseases, similar analysis is also used to identify the pathways in which multiple genes work together, providing possible directions for treatment (Figure 2) (García-Criado et al., 2025). In summary, the analytical method from genes to proteins to metabolites provides practical means for the diagnosis of neuro-metabolic diseases.

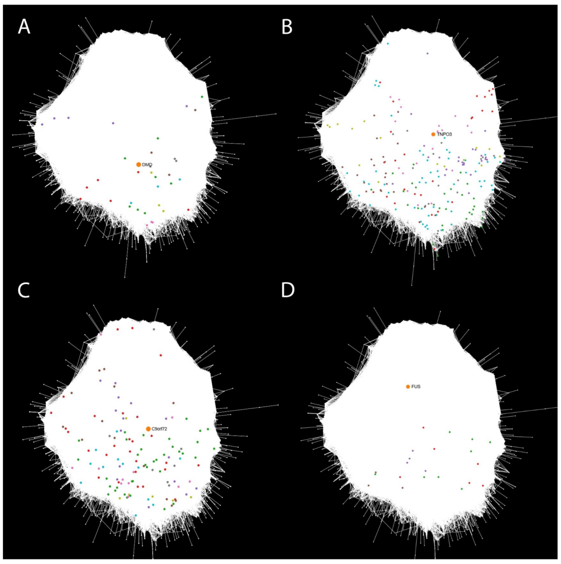

Figure 2 Protein-protein interaction network belonging to the dataset view, based on the union of all expressed genes across all the datasets (white body) (Adopted from García-Criado et al., 2025)

Image caption: Each differentially expressed gene list is represented in different colors, depending on the dataset to which they belonged. Those from the four DMD-related and the two LGMD-related datasets were collapsed into two aggregated DEG lists for visualization clarity. Green: DMD-related datasets; red: LGMD-related datasets; purple: ALS_iN_C9ORF72 dataset; and brown: ALS_fib_FUS dataset. Disease-causal genes (DMD, TNPO3, C9ORF72, and FUS) for all datasets are represented as orange nodes (Adopted from García-Criado et al., 2025)

5.2 Data analysis methods: pathway enrichment, network analysis and artificial intelligence

When analyzing complex data, researchers typically employ two methods: pathway enrichment and network analysis to identify important information. For instance, in the research on Alzheimer's disease, analyzing