Monitoring therapy outcome for neuromuscular disorders

Biomarkers are defined as molecular, cellular or biochemical indicators of physiological or pathological processes. Researchers of the BIO-NMD project endeavoured to extend biomarker applications for validating the outcome of therapeutic approaches.

Neuromuscular diseases (NMDs) are chronic degenerative disorders associated with severe muscle weakness. Extensive research has identified new targets for disease characterisation, early diagnosis and drug development.

However, when it comes to interpreting the success of clinical trials that run for a short time, novel biomarkers are required for endpoint monitoring. Based on this, the EU-funded BIO-NMD project undertook omics-based analyses to identify molecules that could be used as surrogates for therapy outcome. At the same time, the consortium used bioinformatics tools to prioritise genes based on their functions in the selected diseases.

Genetic modifiers were identified that correlated with response to corticosteroid treatment for Duchenne Muscular Dystrophy (DMD) and cyclosporine A for COL6 patients. Over 80 single-nucleotide polymorphisms (SNPs) with potential disease-modification properties entered the validation phase, and 1,600 differentially expressed genes were selected for further exploitation as biomarkers for steroid treatment monitoring.

Whole transcriptional studies led to the discovery of several nuclear long non-coding RNA molecules that regulate dystrophin expression in skeletal muscle. Further dissection of the dystrophin transcription regulation could contribute towards the development of new molecular therapies for dystrophinopathies.

Additionally, proteomics technology was utilised for detection of muscle-derived proteins in the body fluids (serum and plasma) of patients. Using the antibody suspension bead array platform, researchers were able to simultaneously analyse hundreds of proteins in body fluids and identify proteins that correlate with some specific clinical features of DMD. For example, serum levels of MMP-9 were correlated to disease progression in DMD patients compared to healthy controls.

Consortium members also carried out pre-clinical mouse experiments in order to identify novel putative biomarkers and their pathophysiological mechanisms. Markers associated with autophagy and inflammation were identified for COL6 disorders.

The BIO-NMD study biomarkers have the potential to act as sensitive and reliable tools for the prenatal diagnosis of these inherited disorders. At the same time, they could be utilised in drug trials for the prompt prediction of response, thereby providing an evaluation of emerging therapies at reduced cost.