A Metabolic Rescue Index for Monitoring Therapeutic Response in Centronuclear Myopathies

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Résumé

Centronuclear myopathies (CNM) are a clinically and genetically heterogeneous group of rare congenital muscle disorders characterized by myober hypotrophy and progressive muscle weakness. Three principal genetic subtypes are recognized: mutations in MTM1 cause X-linked myotubular myopathy, the most severe form, presenting at birth with profound hypotonia and respiratory failure and frequently fatal in infancy; mutations in BIN1 underlie autosomal recessive CNM of intermediate severity with childhood onset; and mutations in DNM2 cause autosomal dominant CNM, the mildest form, with later onset and a more favorable prognosis.

While therapies targeting DNM2 reduction or BIN1 modulation show promise in murine models, clinical transition is hindered by a lack of non-invasive biomarkers to track muscle recovery without repetitive biopsies. This study identies a serum-based metabolic Rescue Index to monitor disease progression and therapeutic response across these CNM subtypes. By integrating dierential abundance metabolomics from skeletal muscle and serum with transcriptomic and proteomic datasets from wild-type, disease-model, and rescued mice, we applied a reverse matrix analysis to map systemic metabolite shifts back to upstream genetic drivers and enzymatic complexes.

We identify a convergent biomarker pair with robust cross-model reproducibility: N,N,N-trimethyl-alanylproline betaine (TMAP) and trans-4-hydroxyproline. TMAP, a byproduct of MuRF1-mediated myosin degradation, was signicantly elevated in disease states (log2 FC $\approx$ 0.83) and fully reversed upon rescue. Conversely, trans-4-hydroxyproline was markedly suppressed in disease and rose signicantly during recovery (r = –0.85 correlation with muscle mass), reecting P4H-mediated extracellular matrix remodeling. Proteomic proling enabled identication of P4HB (PDI) overexpression as the chaperone-driven mechanism underlying this

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anabolic surge. Our ndings demonstrate that the TMAP/4-hydroxyproline ratio provides a robust, biopsy-free surrogate for muscle structural integrity and metabolic normalization. This
Rescue Index aligns with the common therapeutic signatures of DNM2 reduction and BIN1 overexpression, oering a scalable diagnostic tool for human clinical trials to track real-time pharmacological ecacy.
Overall, this work establishes a metabolomics-driven framework for non-invasive monitoring of therapeutic response in CNM, with the TMAP/4-hydroxyproline ratio serving as a cross-genotype metabolic indicator of structural muscle recovery. The convergent dysregulation of these metabolites across MTM1, BIN1, and DNM2 models positions this Rescue Index as a translationally relevant endpoint for upcoming gene therapy and antisense oligonucleotide trials
in centronuclear myopathies.

Mots-Clés: Centronuclear myopathy, MTM1, BIN1, DNM2, Metabolomics, Biomarkers, Ther, apeutic Rescue, Proteomics.