Skeletal Muscle Biopsy Analysis in Reducing Body Myopathy and Other FHL1-Related Disorders

E. Malfatti MD, PhD[1]

[1] University Paris Est Créteil, Inserm, MUSKETHER LAB U955, IMRB, F-94010 Créteil, France; [2] APHP, Centre de Référence de Pathologie Neuromusculaire Nord-Est-Ile-de-France, Henri Mondor Hospital, Créteil, France.

Abstract

FHL1-related myopathies encompass a heterogeneous group of neuromuscular disorders with overlapping yet distinct clinical and pathological features. To better define their morphological spectrum, we performed a comprehensive histochemical, immunohistochemical, ultrastructural, and immunoelectron microscopy analysis in a large cohort of 18 patients carrying FHL1 mutations. Patients were stratified into two groups based on clinical phenotype: Group 1 included 14 individuals with reducing body myopathy (RBM), while Group 2 comprised three patients with Emery–Dreifuss muscular dystrophy (EDMD) and one patient with hypertrophic cardiomyopathy (HCM) associated with muscular hypertrophy.

Muscle biopsies from Group 1 consistently demonstrated reducing bodies (RBs) associated with cytoplasmic bodies. RBs showed strong immunoreactivity for FHL1, with additional accumulation of desmin, αB-crystallin, and myotilin at their periphery, indicating disruption of cytoskeletal and protein quality control systems. Ultrastructural analysis revealed that RBs consist of electron-dense tubulofilamentous material originating from key sarcomeric structures, including the I-band, M-line, and Z-line, progressively extending between myofibrils and around myonuclei. Immunoelectron microscopy further demonstrated that FHL1 protein is specifically localized within RBs, supporting its central role in aggregate formation.

In contrast, muscle biopsies from Group 2 displayed only mild dystrophic changes without the presence of RBs, and electron microscopy revealed minor, non-specific myofibrillar alterations. Genotype–phenotype correlation showed that Group 1 patients predominantly harbored missense mutations in the second LIM domain of FHL1, whereas Group 2 patients exhibited insertions/deletions or missense mutations in the fourth LIM domain.

Overall, this study expands the morphological characterization of FHL1-related myopathies, highlighting distinct pathological signatures between RBM and non-RBM phenotypes. The findings emphasize the diagnostic value of integrated morphological and molecular analyses and further clarify the specific involvement of FHL1 in reducing body formation.