Nucleolar FRG2 lncRNAs inhibit rRNA transcription and cytoplasmic translation, linking FSHD to dysregulation of muscle-specific protein synthesis

Salsi V, Losi F, Fosso B, et al. Nucleic Acids Res. 2025;53(13):gkaf643.

Presenter: Tzu-Yun Lo **Date/Time:** 2025/12/11 15:20-16:10

Commentator: Dr. H. Sunny Sun **Location:** Room 601, Med College Building

Background: Facioscapulohumeral muscular dystrophy (FSHD) is a hereditary myopathy primarily caused by deletions of the D4Z4 macrosatellite array on chromosome 4q35. These deletions induce local chromatin relaxation and the anomalous expression of proximal genes, including FRG2A. While FRG2A is known to be significantly upregulated in FSHD muscle cells and correlates with disease severity, its biological nature and functional contribution to muscle pathology have remained poorly understood.

Objective: This study aimed to characterize the molecular identity of FRG2A and its paralogs, map their chromatin interaction landscape, and investigate their role in nuclear architecture and gene regulation within the context of FSHD pathogenesis.

Result: The authors established that *FRG2A* belongs to a family of heterochromatin-associated long non-coding RNAs (lncRNAs) that do not encode proteins. Chromatin isolation by RNA purification (ChIRP)-RNA/DNA analysis revealed that these lncRNAs engage in multivalent interactions, acting as a scaffold to bind ribosomal DNA (rDNA) intergenic spacers and centromeric alpha-satellites. High-resolution microscopy and RNase H sensitivity assays confirmed that *FRG2A/B* forms DNA-RNA hybrids (R-loops) within the nucleolus, specifically at the interface of the dense fibrillar component, forming distinct stress-responsive structures termed "Froggy2 Bodies". In FSHD myoblasts, overexpression of *FRG2A* was shown to drive the aberrant clustering of centromeres to the nucleolar periphery, disrupting physiological nucleolus-associated domains (NADs). Functionally, this accumulation represses rDNA transcription, leading to reduced 45S pre-rRNA levels and a global impairment of protein synthesis. Proteomic analysis further highlighted that this translational deficit specifically affects high-demand muscle structural proteins, such as sarcomere components, which are crucial for muscle integrity.

Conclusion: D4Z4-driven upregulation of FRG2 lncRNAs disrupts nucleolar function and suppresses rRNA synthesis, linking chromatin architecture defects to the muscle-specific translational failure observed in FSHD.