How do GGC repeat expansions located in a "non-coding" 5UTR region lead to a myopathy?

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Résumé

Oculo-Pharyngo-Distal Myopathy type 1 (OPDM1, OMIM #164310) is a rare adult-onset genetic neuromuscular disorder characterized by progressive weakness and atrophy of facial, pharyngeal, and distal limbs skeletal muscles. At the histopathological level, OPDM muscle fibers are characterized by the presence of typical intranuclear inclusions, which are p62-positive, but of unknown origin. Thanks to progress in whole genome and long read sequencing, the genetic cause of OPDM1 was recently identified as an abnormal expansion of 50 to 200 GGC repeats in the 5 untranslated region (5UTR) of the LRP12 gene.

Here, we found that these GGC repeats lie within a previously unrecognized small open reading frame (sORF), resulting in their translation into a novel polyGlycine-containing protein. Mass-spectrometry analysis indicates that translation initiation occurs at two near cognate CTG and GTG start codons located upstream of the GGC repeats. Near-cognate start codons are codons differing from the cognate AUG start codon by one nucleotide, but that can nonetheless initiate translation through mispairing with the initiator methionine tRNA. Imporatntly, expression of this novel polyGlycine protein forms p62-positive

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intranuclear inclusions in muscle cells, thus, recapitulating a key feature of this disease.

We are now in the process of determining the toxicity of this polyGlycine protein in cell culture, and future studies will focus on developing antibodies to test its expression in patient tissues, as well as developing an animal model for this disease.

Overall, these findings suggest that OPDM1 is as a repeat expansion disorder caused by expression of a novel and potentially toxic polyGlycine protein.

Mots-Clés: OPDM1, LRP12, GGC repeat expansion, 5UTR, near, cognate start codon, polyGlycine protein, p62, positive intranuclear inclusions, repeat expansion disorder, skeletal muscle weakness, translational initiation