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First Identification of CGG-Repeat Expansions in *LRP12* in Korean Families With Oculopharyngodistal Myopathy Type 1

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Dear Editor,

Oculopharyngodistal myopathy (OPDM) is in the group of autosomal dominant genetic myopathies characterized by progressive ptosis, dysphagia, and distal limb muscle weakness. It is caused by CGG · CCG-repeat expansions in five genes: *LRP12*, *GIPC1*, *NOTCH2NLC*, *RILPL1*, and *ABCD3*.[1-3] The typical pathological features of affected skeletal muscles are chronic myopathic changes with rimmed vacuoles.[2] Short-read next-generation sequencing has contributed significantly to the ability to diagnose genetic myopathies. However, this method has limitations in detecting some regions, such as those with large numbers of repeats and structural variants, which can be overcome using long-read sequencing.[4,5] Here we report two unrelated Korean families with CGG-repeat expansions in *LRP12*, and describe the clinical and pathological features of OPDM type 1 (OPDM1).

The proband in the first family (MF1021) was a 40-year-old male (Fig. 1A, II-1) who initially presented with dysarthria and a nasal voice, which he had experienced since his mid-teens. The patient exhibited ptosis, dysarthria, dysphagia, and muscle weakness in the distal limbs. Mild neck muscle weakness was also observed, but there was no evidence of scoliosis. Serum creatine kinase (CK) was elevated at 416 IU/L, and electromyography (EMG) revealed myopathic changes. One of his younger sisters was a 36-year-old female (Fig. 1A, II-2) who had dysarthria and ptosis, and another was a 34-year-old female (Fig. 1A, II-3) with ptosis, dysarthria, facial muscle weakness, and distal muscle weakness. Muscle biopsy of the proband's biceps brachii revealed multifocal degenerating fibers with focal areas suspicious of rimmed vacuoles. Magnetic resonance imaging (MRI) of the proband revealed fatty infiltration in the bilateral soleus muscles at age 25 years (Supplementary Fig. 1 in the online-only Data Supplement). Based on these clinical and pathological findings, the patients were diagnosed with OPDM. Whole-genome sequencing was performed with the PromethION device (Oxford Nanopore Technologies), and the Straglr software (V.1.5.4) identified a 164-repeat CGG expansion in *LRP12* in the proband. The triple-repeat primed polymerase chain reaction (TP-PCR) confirmed the presence of CGG-repeat expansions in *LRP12* in three affected family members (II-1, II-2, and II-3; Fig. 1B).

The proband in the second family (MF1556) was a 44-year-old male (Fig. 1A, II-1) who first noticed bilateral ptosis in his early 30s. He subsequently developed dysarthria, dysphagia, facial muscle weakness, and distal limb muscle weakness. He did not show neck muscle weakness or scoliosis. His twin brother was a 44-year-old male (Fig. 1A, II-2) who also presented with ptosis and dysarthria. EMG revealed myopathic changes, and serum CK was elevated at 364 IU/L. MRI revealed asymmetric fatty infiltration and atrophy in the distal limb muscles (Supplementary Fig. 1 in the online-only Data Supplement). A biopsy of the left vastus lateralis muscle of patient II-1 demonstrated marked variations in muscle fiber

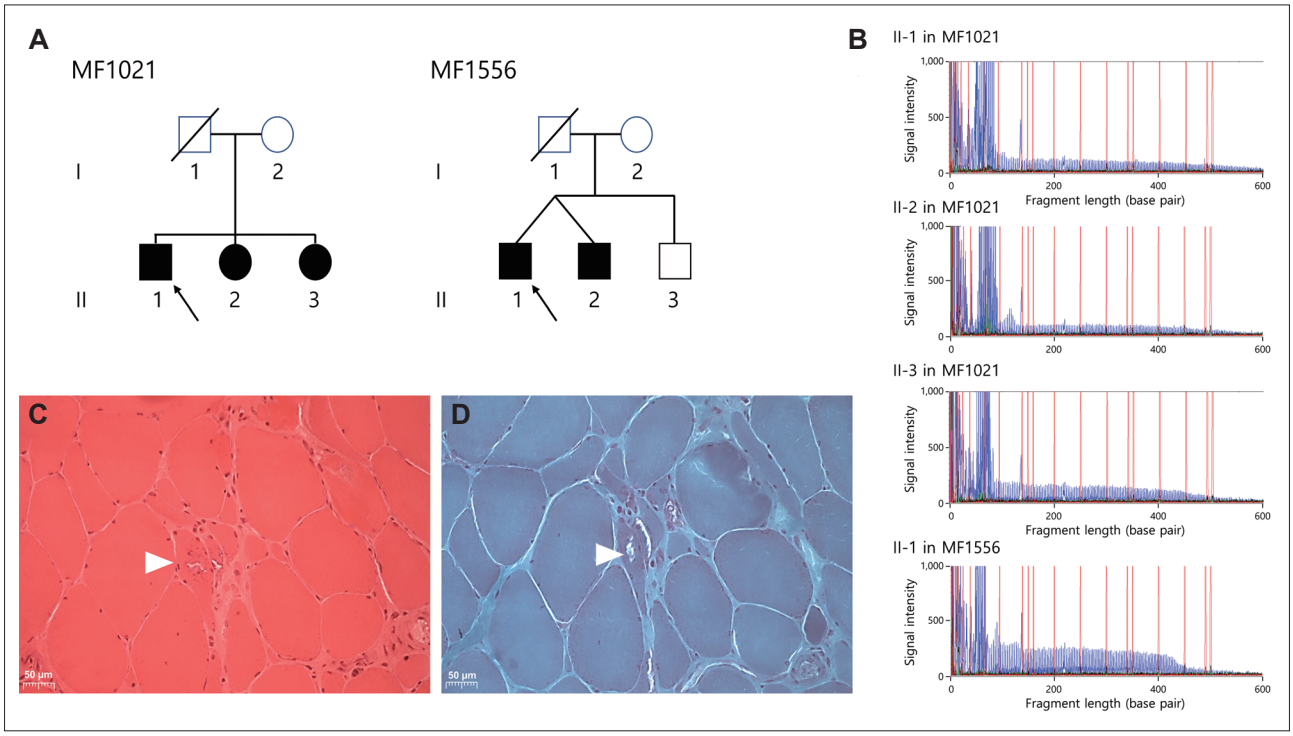

Fig. 1. Pedigree, pathological findings, and genetic analysis. A: Pedigree of two Korean families with oculopharyngodistal myopathy type 1 (arrow, proband; square, male; circle, female; filled, affected; unfilled, unaffected). B: The triple-repeat primed polymerase chain reaction identified CGG-repeat expansions in *LRP12* in patients II-1, II-2, and II-3 from family MF1021, and in patient II-1 from family MF1556. C and D: Pathological analysis of biopsy samples of the vastus lateralis muscle obtained from patient II-1 in MF1556. Hematoxylin and eosin staining showed marked variations in fiber sizes and shapes, and the presence of multiple rimmed vacuoles (white arrowhead). Modified Gömöri trichrome staining also revealed the presence of multiple rimmed vacuoles and increased endomysial fibrosis (white arrowhead).

sizes and several vacuolated fibers (Fig. 1C and D). The proband was clinically and pathologically diagnosed with OPDM. Whole-genome sequencing with the PromethION device identified a 129-repeat CGG expansion in *LRP12*, which was confirmed by TP-PCR (Fig. 1B).

We identified CGG-repeat expansions of the 5' untranslated regions of *LRP12* in two unrelated Korean families with OPDM. The affected individuals exhibited distal limb muscle weakness, ptosis, and pharyngeal weakness of varying severities. Skeletal muscle biopsies revealed chronic myopathic changes and rimmed vacuoles. Lower limb MRI demonstrated asymmetric fatty infiltration and atrophy of the distal lower limbs, especially of the soleus muscles. These clinical and pathological findings were consistent with those of a previous study.[2]

The precise pathomechanism of CGG-repeat expansions in *LRP12* remains unclear. One hypothesized mechanism is RNA-mediated toxicity, where expanded CGG repeats form cytotoxic RNA foci that sequester RNA-binding proteins.[6] Another potential mechanism is a RAN (repeat-associated non-AUG) translation that results in toxic polyglycine proteins that colocalize with the ubiquitinated inclusions.[7] Additionally, similar intranuclear inclusions are seen in biopsy samples of skeletal muscles obtained from patients with OPDM1.

CGG-repeat expansions in *LRP12* were the first identified genetic cause of OPDM1. Subsequent studies found associations with amyotrophic lateral sclerosis and inherited peripheral neuropathy, which broadened the clinical phenotypic spectrum.[8,9] Given this phenotypic diversity, the selection of candidate genes based on clinical and pathological features may result in underdiagnosis, which makes it essential to perform a comprehensive analysis using long-read sequencing so that repeat expansions can be detected. This is the first report of patients with genetically confirmed OPDM1 in South Korea. However, considering the high prevalence of OPDM in Japan and China, which are neighboring countries of South Korea, it is likely that a substantial number of undiagnosed patients remain in the Korean population.[10]

In conclusion, our study has demonstrated the diagnostic utility of long-read sequencing and highlighted the importance of considering OPDM1 in the differential diagnosis of adult-onset myopathies with rimmed vacuoles and distal muscle involvement.

Supplementary Materials

The online-only Data Supplement is available with this arti-

cle at https://doi.org/10.3988/jcn.2025.0255.

Ethics Statement

This study was approved by the Institutional Review Board of Gangnam Severance Hospital, Korea (approval number: 3-2025-0041).

Availability of Data and Material

The data supporting the findings of this study are available in the supplementary material.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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REFERENCES

1. Ishiura H, Shibata S, Yoshimura J, Suzuki Y, Qu W, Doi K, et al. Noncoding CGG repeat expansions in neuronal intranuclear inclusion disease, oculopharyngodistal myopathy and an overlapping disease. *Nat Genet* 2019;51:1222-1232.
2. Kumutpongpanich T, Ogasawara M, Ozaki A, Ishiura H, Tsuji S, Minami N, et al. Clinicopathologic features of oculopharyngodistal myopathy with LRP12 CGG repeat expansions compared with other oculopharyngodistal myopathy subtypes. *JAMA Neurol* 2021;78:853-863.
3. Cortese A, Beecroft SJ, Facchini S, Curro R, Cabrera-Serrano M, Stevanovski I, et al. A CCG expansion in ABCD3 causes oculopharyngodistal myopathy in individuals of European ancestry. *Nat Commun* 2024;15:6327.
4. Owusu R, Savarese M. Long-read sequencing improves diagnostic rate in neuromuscular disorders. *Acta Myol* 2023;42:123-128.
5. Bruels CC, Littel HR, Daugherty AL, Stafki S, Estrella EA, McGaughy ES, et al. Diagnostic capabilities of nanopore long-read sequencing in muscular dystrophy. *Ann Clin Transl Neurol* 2022;9:1302-1309.
6. Hagerman PJ, Hagerman RJ. The fragile-X premutation: a maturing perspective. *Am J Hum Genet* 2004;74:805-816.
7. Cleary JD, Pattamatta A, Ranum LPW. Repeat-associated non-ATG (RAN) translation. *J Biol Chem* 2018;293:16127-16141.
8. Kume K, Kurashige T, Muguruma K, Morino H, Tada Y, Kikumoto M, et al. CGG repeat expansion in LRP12 in amyotrophic lateral sclerosis. *Am J Hum Genet* 2023;110:1086-1097.
9. Hobara T, Ando M, Higuchi Y, Yuan JH, Yoshimura A, Kojima F, et al. Linking LRP12 CGG repeat expansion to inherited peripheral neuropathy. *J Neurol Neurosurg Psychiatry* 2025;96:140-149.
10. Shimizu T, Ishiura H, Hara M, Shibata S, Unuma A, Kubota A, et al. Expanded clinical spectrum of oculopharyngodistal myopathy type 1. *Muscle Nerve* 2022;66:679-685.