Sir,

Calpainopathy belongs to a group of limb-girdle muscular dystrophies (LGMD), characterized by proximal muscle weakness. Calpainopathy or LGMD2A is an autosomal recessive disease caused by mutations in the calpain-3 gene ($\text{CAPN3}$).\(^1\)

We report the case of a 16-year-old male patient with a myopathy with proximal muscle weakness. He started tiptoeing up, at the age of 4. At 13-year-old, he began to have difficulty climbing stairs, incorporating from the ground and running, being referred to the neurologist. Physical examination showed muscle weakness of shoulder and pelvic girdle, positive Gower’s sign, lumbar lordosis, and joint contractions. CK was elevated (7341 UI/L). Electromyography showed myopathic pattern, muscle biopsy, a dystrophic pattern, and the immunohistochemical analysis showed a lower intensity of staining with anti-DYS-3 antibody (Dp427m-dystrophin protein) [Figure 1a].

These results focused the diagnosis on the Becker muscular dystrophy (BMD), and treatment with corticosteroids was indicated. He was operated for bilateral tendon lengthening.

A multiplex ligation-dependent probe amplification (MLPA) test was carried out to detect duplications and deletions in the dystrophin gene ($\text{DMD}$). MLPA results confirmed the diagnosis which revealed 49 ± 3 CAG repeats (normal range 9–36). Kennedy’s disease (spinobulbar muscular atrophy [SBMA]) is a rare X-linked recessive neurodegenerative disorder characterized by degeneration of lower motor neurons and is caused by CAG trinucleotide repeat expansion in the androgen receptor gene on chromosome Xq11-12.\(^2\)

It is characterized by progressive atrophy and weakness of limb and bulbar muscles with tongue atrophy and chin fasciculations and with onset in the 3rd–5th decades. Patients may have endocrinological abnormalities in the form of gynecomastia, testicular atrophy, and diabetes mellitus.\(^3\)

It is important to differentiate Kennedy’s disease from other neuromuscular disorders as several disorders of varying severity and outcomes resemble SBMA. On electrophysiological studies, CMAP amplitudes may be low. Most patients have low amplitude or absent SNAPs, which reflect the association of Kennedy’s disease with degeneration of the dorsal root ganglia. Currently, there is no cure for Kennedy’s disease, and treatment is mainly symptomatic and supportive.\(^4\)

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There are no conflicts of interest.

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were normal. The study continued by next-generation sequencing (NGS) analysis, using a commercial panel of a clinical exome (TruSight One of Illumina®). No point mutations in the DMD gene were found and 23 genes associated with LGMD and Emery-Dreifuss muscular dystrophy were analyzed: TRIM32/DES/SGCB/FKTN/CAV3/FKRP/SGCG/SGCD/DNAJB6/SGCA/CAPN3/TTN/ANOS/DYSF/PLEC/DAG1/EMD/LMNA/MYOT/TCAP/POMGNT1/POMT1/POMT2. The patient had two mutations in heterozygosity in the CAPN3 gene: c. 550delA;p.Thr184Argfs*36 and c. 3261_3262delAGinsTCATCT;p.Arg788Serfs*14 (NM_000070). Sanger sequencing confirmed the mutations detected in the patient and identified the mutations in the father and the mother, respectively.

An abnormal calpain-3 protein expression was demonstrated in the skeletal muscle biopsy of the patient by Western blot [Figure 1b], and the diagnostic of calpainopathy was confirmed. Both mutations in the CAPN3 gene cause a change in the reading frame (frameshift mutation), leading to a premature stop codon and calpain-3 abnormal protein. They have been described previously as LGMD2A pathogenic in several studies.[2,3]

The wide variety of muscular dystrophies and common clinical manifestations makes necessary the immunohistochemical studies, immunoblotting, and molecular genetics to reach the definitive diagnosis of these pathologies. We report a case with a diagnostic suspicion of BMD, where the incorporation of NGS has been essential for the diagnosis of calpainopathy. NGS enables the screening of many genes at once and was chosen since the classical Sanger method is laborious and time-consuming. Mutation identification is the necessary approach to an upcoming gene therapy.[4]

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