**Supplementary Material**

1. **METHODS**

Informed consent was obtained to publish the clinical and genetic data of the subjects.

The Proband (III-1) underwent molecular evaluation in 2017 using the Invitae Comprehensive Neuromuscular Disorders Panel (Invitae, San Francisco, CA), which included 107 genes that are associated with inherited neuromuscular disorders, including muscular dystrophies, myopathies, and congenital myasthenic syndromes. Proband’s mother and sister had targeted genetic testing for the variants detected in the proband in the same laboratory. Subject III-10 and her son, IV-6, underwent molecular evaluation in 2018 and 2019, respectively, using the Invitae Comprehensive Myopathy Panel, which included 55 genes that are associated with inherited myopathies.

Exome sequencing (ES) of subject III-1 was performed in 2019 through a commercial diagnostic laboratory (GeneDx, Gaithersburg, MD) to rule out the contribution of additional genetic factors to his muscle disease. Exonic regions and flanking splice junctions were captured using a proprietary capture system developed by GeneDx for next-generation sequencing with CNV calling. The enriched targets were massively parallel sequenced using an Illumina HiSeq 2000 sequencing system with 100 bp paired end‐reads. Bi-Bidirectional sequence data were aligned to human genome build GRCh37/UCSC hg19. The mean depth of coverage was ×142 with 98.8% exome coverage by at least 10 sequence reads, including the entire ANO5 coding region. ANO5 variant was confirmed by capillary sequencing and classified according to the American College of Medical Genetics guidelines.

1. **FAMILY HISTORY**

The Proband’s 65-year-old mother (II-2) is of Caucasian descent and his father (II-1) is of Persian ancestry (**Fig.1**). His mother had expanding cemento-ossifying fibromas in her jaw (**Fig. 3 F&G**) requiring massive debulking at age 45 years, recurrent bone fractures (**Fig.3 D&E**), as well as a long history of muscle cramps. The Proband has two brothers (III-2 and III-3) and one sister (III-4). His sister was diagnosed with massive cemento-ossifying fibromas of the jaw requiring a debulking surgery as an infant but exhibited no muscle symptoms. One of Proband’s brothers (III-3) as well as his 17-year-old son (IV-3) had jaw cemento-ossifying fibromas and recurrent episodes of muscle cramps. Proband’s mother had three sisters. Her 71-year-old sister (II-3) had cemento-ossifying fibromas and muscle cramps requiring follow up and evaluation at a different neuromuscular clinic. Her second sister (II-4), who is the mother of subject III-10, had cemento-ossifying fibromas and recurrent muscle cramps. She died due to sepsis complicating osteomyelitis of her jaw lesion. Her 74-year-old sister (II-5) had cemento-ossifying fibromas but no muscle symptoms; her son (III-11) had cemento-ossifying fibromas and exhibited severe muscle cramps; his clinical course was complicated with alcoholism, which was reportedly started as a self-treatment of his severe pains and ultimately caused his death at 50 years old.