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Homozygosity of a Founder Variant c.1508dupC in *DOK7* Causes Congenital Myasthenia With Variable Severity

Johanna Palmio, MD, PhD, Panu Kiviranta, MD, PhD, Päivi H. Hartikainen, MD, PhD, Pirjo Isohanni, MD, PhD, Mari Auranen, MD, PhD, Karoliina Videman, MD, Sini Penttilä, PhD, Sara Lehtinen, MSc, Jarkko Kirjavainen, MD, PhD, Susanna Hintikka, MD, Katriina Paloviita, Janna Saarela, PhD, and Bjarne Udd

Correspondence
Dr. Palmio
johanna.palmio@tuni.fi

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Abstract

Background and Objectives

Description of 15 patients with the same variant in *DOK7* causing congenital myasthenic syndrome (CMS).

Methods

Nine adult and 6 pediatric patients were studied with molecular genetic and clinical investigations.

Results

All patients were identified with the c.1508dupC variant in *DOK7*, of whom 13 were homozygous and 2 patients compound heterozygous. Only 2 patients had limb girdle phenotype, while all adult patients also had ptosis, ophthalmoplegia, facial weakness, as well as inspiratory stridor. Pediatric patients had severe respiratory insufficiency and feeding difficulties at birth.

Discussion

The disease severity in our patients varied extensively from ventilator or wheelchair dependence to mild facial weakness, ptosis, and ophthalmoparesis. Most of the patients had normal transmission in conventional 3 Hz stimulation electrophysiologic studies, making the diagnosis of CMS challenging. Our cohort of adult and pediatric patients expands the phenotype of DOK7 CMS and shows the importance of correct and early diagnosis.

Introduction

Congenital myasthenic syndromes (CMS) are a rare and heterogeneous group of inherited disorders with impaired neuromuscular transmission at the motor endplate.[1,2] Traditionally, the CMS have been classified according to the location of the defective protein; presynaptic, synaptic, or postsynaptic. With the growing number of CMS-causing genes being identified, other rarer subtypes have emerged[3]; to date, at least 30 genes have been reported, with most of these affecting the postsynaptic neuromuscular junction structure and function.[1-3] The symptoms present at birth or in early childhood and are usually characterized by ptosis, exercise-induced weakness, and fatigability. Variants in the Docking Protein 7 gene, *DOK7*, are among the most common causes of CMS and have frequently been associated with a limb-girdle or axial phenotype.[4-7] The final molecular genetic diagnosis of CMS is frequently delayed

From the Neuromuscular Research Center (J.P., S.P., B.U.), Tampere University and University Hospital, Neurology; The Finnish Medical Society Duodecim (P.K.), Helsinki; Department of Pediatrics (P.K.), Kuopio University Hospital, and University of Eastern Finland Kuopio; Neurocenter (P.H.H.), Neurology, Kuopio University Hospital; Department of Child Neurology (P.I.), Children's Hospital, Pediatric Research Center, University of Helsinki and Helsinki University Hospital; Research Programs Unit (P.I.), Stem Cells and Metabolism, University of Helsinki; Clinical Neurosciences (M.A.), Neurology, University of Helsinki and Helsinki University Hospital; Department of Pediatric Neurology (K.V.); Department of Genetics (S.L.), Fimlab Laboratories, Tampere University Hospital; Department of Pediatric Neurology (J.K.), Kuopio University Hospital; Department of Neurology (S.H., K.P.), Central Finland Central Hospital, Jyväskylä; Institute for Molecular Medicine Finland FIMM (J.S.), University Helsinki, Finland; Centre for Molecular Medicine Norway (J.S.), University of Oslo, Norway; Folkhälsan Institute of Genetics and the Department of Medical Genetics (B.U.), Haartman Institute, University of Helsinki; and Department of Neurology (B.U.), Vaasa Central Hospital, Finland.

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Glossary

CMS = congenital myasthenic syndrome.

due to a lack of clear fluctuations of symptoms or absent myasthenic findings in electromyographic transmission studies. However, the correct molecular genetic diagnosis is essential because of the targeted treatment options available for the patients.[7,8]

We report 13 patients with a homozygous variant c.1508dupC in *DOK7* and 2 patients with compound heterozygosity, having the same mutation in 1 allele. Despite the genotypic similarity, their disease severity was highly variable.

Methods

We identified 15 Finnish patients from nonconsanguineous parents (P1–P15) with *DOK7* variants (Figure, Table 1). Two patients (P4, P5) were siblings, whereas others were unrelated and had no other similarly diagnosed family members. However, 1 patient (P2) had had 3 siblings who all had died within few hours after birth in the 60's, P8 had had a brother who had died in his thirties due to unknown myopathy, and P15 had had a sister (born in 2017), who died at 6 days of age due to hypoplastic lungs, eventration of the diaphragm, and following respiratory insufficiency.

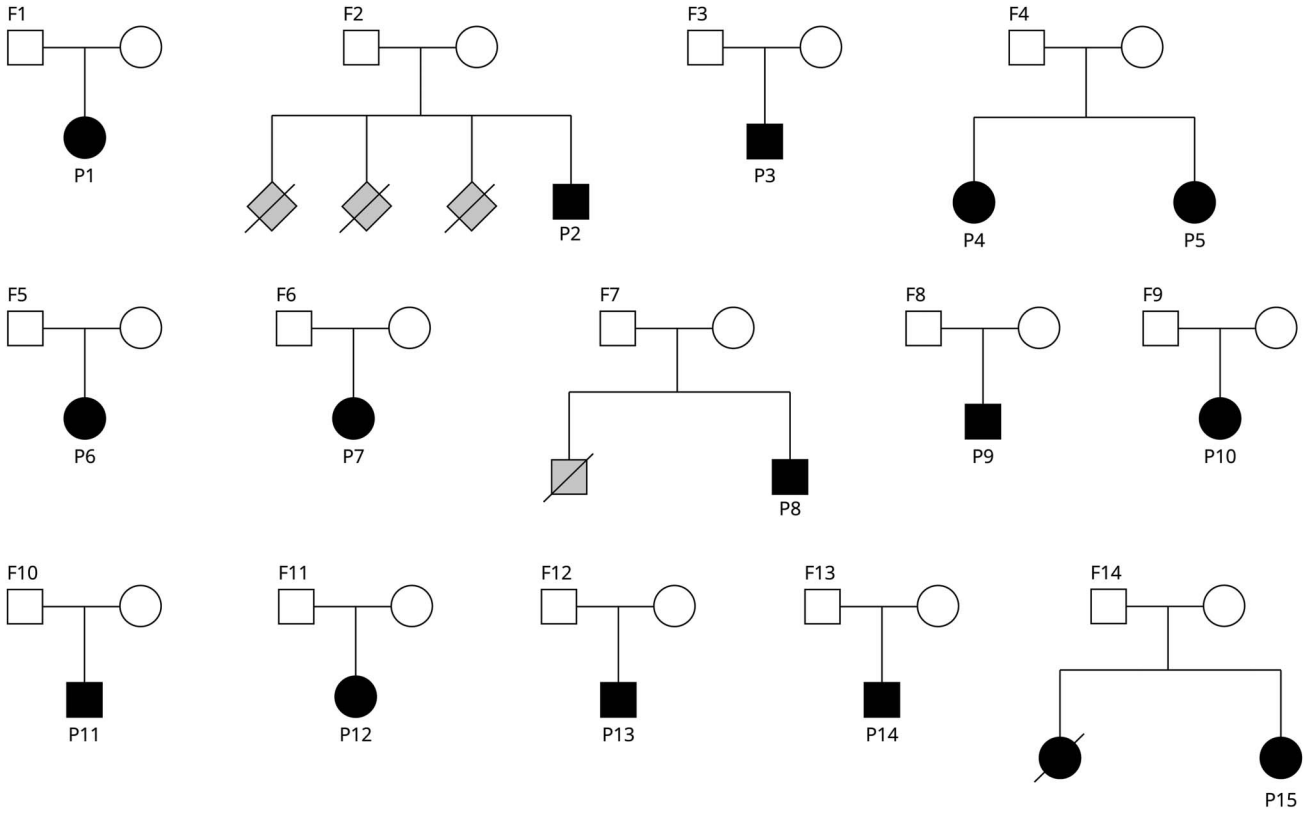
All patients had been clinically examined, their medical and family histories taken, and their muscle examination evaluated by a neurologist or a child neurologist. Eleven patients had undergone electrophysiologic examinations including nerve conduction studies, needle EMG, and 3 Hz stimulation studies. Muscle biopsy was available in 8 and muscle imaging by MRI in 4 patients.

Genomic DNA was extracted from venous blood according to standard procedures. The variants in *DOK7* were identified by Sanger sequencing of exon 7 or by targeted exome sequencing.[9] In addition, P9 and P15 were investigated by whole-exome sequencing.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the Research Ethics Committee of the Pirkanmaa Hospital District (R01185). The study was performed according to the Declaration of Helsinki.

Figure Pedigrees of the Families



Black indicates confirmed DOK7 CMS; gray indicates affected sibling without molecular genetic confirmation.

Table 1 Clinical Characteristics of the Patients

	Age at onset	Age at diagnosis	Ptosis	Ophthal-moplegia	Muscle weakness	Other	Fatigability	Respiratory insufficiency	Medication
Adult patients									
P1	0	31 y	Yes, at birth	Yes	Generalized, severe proximal LL, facial	High-arched palate	Yes, WCB at age 26 y	Inspiratory stridor, childhood asthma, NIV at age 22 y	Ephedrine, salbutamol
P2	0	43 y	Yes, at birth	Yes	Generalized, slim limb muscles, facial	Kyphoscoliosis	Yes, ambulant	Congenital stridor, tracheostomy (0–1.5 y), severe sleep apnea, BiPAP	Ephedrine, salbutamol
P3	0	27 y	Yes, at birth	Yes	Mild facial, no limb weakness	—	Mild during heavy exercise	Inspiratory stridor when exercising	No need for medication
P4	0	42 y	Yes, at birth	Yes	Mild facial	Kyphoscoliosis hyperlordosis, high-arched palate	Not clear, ambulant	Inspiratory stridor	No need for medication
P5	0	59 y	Yes, at birth	Yes	Neck muscles, dropped head, facial, mild generalized	Kyphoscoliosis, high-arched palate	Mild UL, ambulant	Inspiratory stridor, at age 54 y, VPAP	Salbutamol
P6	0	23 y	Yes, at birth	Yes	Marked facial	Kyphoscoliosis, operated at 16 y	Mild during exercise, ambulant	Mild inspiratory stridor	Citalopram
P7	0	25 y	Yes, at 10 mo	Yes	Generalized mild muscle and facial	Congenital laryngomalacia, dysphagia	Yes	Inspiratory stridor, mild restriction	Salbutamol
P8	Childhood	41 y	Yes (plastic surgery)	Yes	Generalized muscle and facial	Kyphoscoliosis, high-arched palate	Yes, ambulant	Severe, respiratory failure at age 41 y, NIV at present	Ephedrine, salbutamol
P9	0	35 y	Yes, at birth	Yes	Moderate proximal and facial	Scoliosis operated at 11y	Yes, walking aid (rollator), walking distance 200 m	Severe, tracheostomy at 5 mo, need for persistent ventilatory support	Salbutamol
Pediatric patients									
P10	0	3 mo	Yes, at birth	No	Severe feeding difficulties (PEG)	—	Not clear	Severe at birth, tracheostomy, ventilator dependent during infections	Salbutamol
P11	0	2 y	Yes l.sin., at birth	No	Severe feeding difficulties (PEG 4 mo–6 y)	Delayed motor milestones	Yes	Severe at birth, tracheostomy (0–6 mo), sleep apnea, NIV	Salbutamol
P12	0	3.5 y	Yes, 2 y	No	Severe feeding difficulties (PEG 2 mo–3 y)	—	Mild	Severe inspiratory stridor, tracheostomy (3 mo–2y)	Salbutamol
P13	0	4 y	Yes, at birth	No	No	Mild motor development delay	Yes, mild	Severe, tracheostomy (0–6 mo), stridor; No at present	Salbutamol
P14	0	9 mo	Yes, at 7 mo	Yes, partial	No	—	Yes > no with sufficient medication	Severe, tracheostomy (3 wk–1.5 y)	Salbutamol
P15	0	Antenatal	Yes, at birth	No	Severe feeding difficulties (nasogastric tube)	Hydrocephalus	Yes	Severe, tracheostomy (1 mo -)	Salbutamol

Abbreviations: BiPAP = bi-level positive airway pressure; F = female; LL = lower limbs; M = male; NIV = noninvasive ventilator; PEG = percutaneous endoscopic gastrostomy; UL = upper limbs; VPAP = variable positive airway pressure; WCB = wheelchair bound.

Data Availability

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

Results

The first symptoms were present at birth or in very early childhood in all patients. The presenting and consistent findings were ptosis and respiratory symptoms.

Adult Patients

The age at last examination was 25–68 years in the adult cohort. Severity of symptoms varied between the patients in adulthood, but all had some degree of ptosis, and all had ophthalmoplegia severely restricting eye movements, especially vertically (Table 1). The mildest symptoms of the disease were noted in P3 who, in addition to ptosis and ophthalmoplegia, had mild facial but no limb muscle weakness. Mild fatigability as well as inspiratory stridor were present only during exercise in P3. Mild-to-moderate facial weakness was observed in all patients, and kyphoscoliosis and high-arched palate were frequent findings. P1 showed the most severe long-term symptoms and had been wheelchair bound for a decade at age 38 years. However, when the molecular genetic diagnosis was confirmed and relevant treatment was initiated, she was again able to walk for short distances. P8 presented with respiratory failure at age 41 years. He had ptosis and myopathic facies that led to initial diagnosis of myasthenia gravis. However, antibody testing was negative, and initial treatment was unsuccessful. Electrophysiology showed postsynaptic defect, and a correct molecular diagnosis of CMS was promptly achieved. P9 had mild stable proximal weakness and needed a walker for walking. All patients benefited from CMS pharmacotherapy so that fatigability was less severe and exertion more tolerated. Mostly used medications were salbutamol (4 mg twice a day) and ephedrine (ad 100 mg daily).

All adult patients experienced inspiratory stridor since birth or early childhood with variable severity (Table 1). Five of them were examined by spirometry with only 1 having markedly reduced pulmonary functions. P9 had the most severe respiratory symptoms and needed persistent ventilatory

Table 2 Neuromuscular Investigations

Patients	Transmission EMG	CK levels	Muscle histology	Spirometry (L)	Muscle imaging
P1	Normal	Normal	Normal	VC, FVC > 3	Fatty degenerative changes
P2	Myasthenic findings	Normal	Normal	Not done	Not done
P3	No myasthenic findings; mild myopathic changes in left orbicularis oculi	3xUNL	Mild myopathic changes	VC 4.79, FVC 4.77	No abnormal changes
P4	Mild neurogenic, no myasthenic findings	Normal	Normal	FVC 1.54 (PEF 109)	No abnormal changes
P5	Normal	Normal	Mild myopathic changes	FVC > 3	No abnormal changes
P6	Normal	Normal	Not done	Not done	Not done
P7	Normal	Normal	Normal	FEV1 2.52, FVC 2.89	Not done
P8	Postsynaptic transmission defect	Normal	Not done	Not done	Not done
P9	Postsynaptic transmission defect	Normal	Fibre type disproportion (type 2 predominance)	Not done Ventilatory support with trilogy	Not done
P10	Normal	Normal	Normal or mild abnormalities in oxidative stains	Not done	Not done
P11	Not done	Normal	Not done	Not done	Not done
P12	Normal	Normal	Not done	Not done	Not done
P13	Not done	Not done	Not done	Not done	Not done
P14	Not done	Not done	Not done	Not done	Not done
P15	Not done	Normal	Not done	Not done	Not done

Abbreviations: CK = creatine kinase; FVC = forced vital capacity; PEF = peak expiratory flow; UNL = upper normal limit; VC = vital capacity.

support, P8 needed noninvasive ventilator during nighttime due to sleep apnea. Muscle histology was available from 7 patients and muscle imaging from 4 patients. The findings were normal or unspecific (Table 2).

Pediatric Patients

The age at last examination was between 0 and 9 years in the pediatric cohort. All patients had severe respiratory insufficiency after birth. The presenting symptom was inspiratory stridor, and respiratory failure required intubation and mechanical ventilation. Attempts to wean off these infants from ventilator were unsuccessful, and therefore, all of them required tracheostomy. Respiratory support was needed until the respiratory functions improved between ages 3 months and 1 year when decannulation was successful in 4/6 patients. P15 still needed mechanical ventilation at the age of 3 months (current situation) and P10 during infections (Table 1). Feeding difficulties were more persistent requiring feeding via nasogastric tube, and 4/6 children also required percutaneous endoscopic gastrostomy (PEG) tube feeding. Ptosis was present also in the children, either already at birth or before 2 years of age, but ophthalmoparesis has not yet been observed except for 1 patient. Salbutamol (0.1–0.3 mg/kg daily) was used for all pediatric patients after establishing the molecular diagnosis. After the initiation of medication, the patients showed clinical improvement, were less fatigued, could be weaned from tracheostomy and PEG, and continued motor development similar to their peers. However, medication had no effect on ocular symptoms.

Electrophysiologic Findings

Three of 11 patients examined showed myasthenic findings in 3 Hz stimulation studies (Table 2). All other transmission studies showed normal or unspecific results. Single-fiber EMG was not performed in the patients with normal 3 Hz stimulation results.

Molecular Genetics

The final CMS diagnosis with molecular genetic confirmation was obtained during adulthood in P1–P9, whereas P10–P15 were pediatric patients. The diagnostic delay was 23–59 years in the adult patients and 3 months to 4 years in the pediatric patients. In addition, P15 had genetically confirmed antenatal diagnosis, and the genetic diagnosis of the deceased sister was confirmed at the same occasion.

Thirteen patients were found to harbor the same homozygous duplication/frameshift variant c.1508dupC p.(Pro504SerfsTer15) (according to transcript NM_173660.5) in the *DOK7* gene. The duplication introduces 13 new amino acids to the end of the coding sequence, thus elongating the transcript and protein. Furthermore, P9 and P15 were compound heterozygous with c.1508dupC and c.1378dupC p.(Gln460ProfsTer59), identified by exome sequencing. Compound heterozygosity of c.1508dupC and c.1378dupC has been previously reported in a Finnish patient with CMS.[4]

Discussion

Our cohort of 15 DOK7 CMS patients showed consistent features of ptosis, ophthalmoplegia, and respiratory symptoms, although the severity of the muscle symptoms varied extensively. The phenotype frequently reported in DOK7 CMS, limb-girdle pattern or axial distribution of weakness,[4,6,7,10-14] was found in only 2 of our patients. The diagnostic delay was long, even several decades in the adult patients causing a similar delay in the initiation of proper treatment.[11]

All 6 pediatric patients presented with a consistent phenotype of severe respiratory and feeding difficulties at birth requiring tracheostomy and often PEG. Fatigability was not a key finding, or it appeared more clearly later in life.[15] More typically, previously reported children with DOK7 CMS have shown first symptoms as walking difficulties in early childhood with limb-girdle or axial weakness and fatigability.[10-12,15,16] However, some studies have found congenital stridor and feeding difficulties as the only presenting symptoms in DOK7 CMS, and these features can also be considered as clues to early diagnosis.[13,15]

Fatigability and inspiratory stridor or respiratory insufficiency constituted the most disabling symptoms of our adult patients. Ophthalmoplegia with severely restricted eye movements was not a feature at birth but was present in all adult patients. It developed gradually during childhood years, although data on the exact year of onset were not available for every patient because all patients were not regularly followed up after the initial investigations after birth. This phenotypic feature may be related to the c.1508dupC variant because it is not typically found in other DOK7 CMS cases.[4]

The long diagnostic delay in the adults was mainly due to the misdiagnosis (e.g., congenital myopathy or mitochondrial myopathy) and the lack of possibilities in the genetic diagnosis in the earlier years. In addition, electrophysiologic studies might fail to show myasthenic findings if not performed in a weak muscle. It is worth noting that after seemingly stable period, there is a possibility of an adult-onset respiratory failure that needs careful monitoring in DOK7 CMS patients.

In the Finnish population, the c.1508dupC variant has an allele frequency of 0.003170, which is 10 times higher than the average frequency (gnomAD database). According to the Hardy-Weinberg equation, it is estimated that with the frequency of 0.003170, there could be approximately 55 homozygotes in Finland, and thus, many cases remain to be identified. Given the wide variation in symptom severity, there may be a diagnostic gap because mild phenotypes may go undiagnosed and severe phenotypes lead to antenatal or neonatal mortality. The c.1508dupC is apparently a Finnish founder variant. There are no epidemiologic data

on the overall prevalence or genetic background of CMS in Finland, but based on the current report, it seems that *DOK7* variants are the most common causes of CMS in Finland. We recommend investigating this variant among other CMS genes in newborns who need tracheostomy for long-term respiratory support due to nonpulmonary disease.

Regardless of the identical homozygous variant in our patients, the severity of symptoms varied extensively from neonatal severe respiratory insufficiency and feeding difficulties to mild fatigability and normal ambulation in the middle age. Most of our patients had stridor and ptosis, often accompanied with ophthalmoplegia, a combination of symptoms suggestive of CMS. The variable phenotype of the disease and the possibility of normal transmission in conventional 3 Hz stimulation electrophysiologic studies make the diagnosis of CMS challenging, and thus, molecular genetic studies are essential. Our cohort of adult and pediatric patients expands the phenotype of DOK7 CMS and underlines the importance of early diagnosis to ensure proper treatment.

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Disclosure

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Appendix Authors

Name	Location	Contribution
Johanna Palmio, MD, PhD	Neuromuscular Research Center, Tampere University and University Hospital, Neurology, Finland	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Panu Kiviranta, MD, PhD	The Finnish Medical Society Duodecim, Helsinki; Department of Pediatrics, Kuopio University Hospital, and University of Eastern Finland Kuopio, Finland	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data
Päivi H. Hartikainen, MD, PhD	Neurocenter, Neurology, Kuopio University Hospital, Finland	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data
Pirjo Isohanni, MD, PhD	Department of Child Neurology, Children's Hospital, Pediatric Research Center, University of Helsinki and Helsinki University Hospital; Research Programs Unit, Stem cells and Metabolism, University of Helsinki, Finland	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data
Mari Auranen, MD, PhD	Clinical Neurosciences, Neurology, University of Helsinki and Helsinki University Hospital, Finland	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data
Karoliina Videman, MD	Department of Pediatric Neurology, Tampere University Hospital, Finland	Drafting/revision of the article for content, including medical writing for content; analysis or interpretation of data
Sini Penttilä, PhD	Neuromuscular Research Center, Tampere University and University Hospital, Neurology, Finland	Drafting/revision of the article for content, including medical writing for content; analysis or interpretation of data
Sara Lehtinen, MSc	Department of Genetics, Fimlab Laboratories, Tampere University Hospital, Finland	Drafting/revision of the article for content, including medical writing for content; analysis or interpretation of data
Jarkko Kirjavainen, MD, PhD	Department of Pediatric Neurology, Kuopio University Hospital, Finland	Drafting/revision of the article for content, including medical writing for content; analysis or interpretation of data
Susanna Hintikka, MD	Department of Neurology, Central Finland Central Hospital, Jyväskylä, Finland	Major role in the acquisition of data; analysis or interpretation of data
Katriina Paloviita	Department of Neurology, Central Finland Central Hospital, Jyväskylä, Finland	Major role in the acquisition of data; analysis or interpretation of data
Janna Saarela, PhD	Institute for Molecular Medicine Finland FIMM, University Helsinki, Finland; Centre for Molecular Medicine Norway, University of Oslo, Norway	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data
Bjarne Udd	Neuromuscular Research Center, Tampere University and University Hospital, Neurology; Folkhälsan Institute of Genetics and the Department of Medical Genetics, Haartman Institute, University of Helsinki; Department of Neurology, Vaasa Central Hospital, Finland	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

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