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Short Communication

Early-Onset Autosomal Dominant Myopathy with Vacuolated Fibers and Tubular Aggregates but No Periodic Paralysis, in a Patient with the c.1583G>A (p.R528H) mutation in the *CACNA1S* Gene

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Abstract. Dominant mutations in *CACNA1S* gene mainly causes hypokalemic periodic paralysis (PP)(hypoPP). A 68-year-old male proband developed a progressive proximal weakness from the age of 35. Muscle biopsy showed atrophic fibers with vacuoles containing tubular aggregates. Exome sequencing revealed a heterozygous p.R528H (c.1583G>A) mutation in the *CACNA1S* gene. *CACNA1S*-related HypoPP evolving to persistent myopathy in late adulthood is a well-known clinical condition. However, isolated progressive myopathy (without PP) was only exceptionally reported and never with an early onset. Reporting a case of early onset *CACNA1S*-related myopathy in a patient with no HypoPP we intend to alert clinicians to consider it in the differential diagnosis of younger adult-onset myopathies especially when featuring vacuolar changes.

Keywords: Hypokalemic periodic palsy, early onset myopathy, vacuolar myopathy, *CACNA1S*

INTRODUCTION

The *CACNA1S* ($Ca_v1.1$) gene encodes the pore-forming subunit of the dihydropyridine receptor (DHPR) located on the skeletal muscle T-tubules. DHPR is a voltage-gated L-type Ca^{2+} channel responsible for the process of excitation–contraction coupling (ECC) by interacting with the ryanodine receptor (RYR1) at the triad: this interplay triggers muscle contraction. Mutations in the *CACNA1S* gene result in a paradoxical depolarization that reduces fiber excitability and contractility during an attack of HypoPP caused by an anomalous gating pore leakage current in mutant CaV1.1 channels [1, 2]. Dominant mutations in the *CACNA1S* gene are known to cause hypokalemic periodic paralysis (HypoPP) and malignant hyperthermia (MHS5) [3–6]. More

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recently, dominant and recessive mutations in the *CACNA1S* gene have been linked to a novel class of congenital myopathies and to a late-onset myopathy without HypoPP [7, 8]. In describing progressive early onset myopathy with heterozygous *CACNA1S* mutation we aim to expand the phenotypical spectrum of *CACNA1S* gene mutations beyond strict channelopathies to include other myopathies.

CASE REPORT

The proband (PII.2), a male Caucasian patient aged 68, coming from a family of 5 siblings (Fig. 1), without evidence of consanguinity, was referred to our tertiary center in 2020, for progressive weakness of the four limbs evolving since the age of 35. The patient had an asymptomatic 49-year-old daughter, a living 58-year-old brother (who was also asymptomatic), a deceased affected brother (PII.3), and a deceased sister. The patient's mother was wheelchair-bound from the age of 55 and had presented attacks of transient paralysis compatible with a diagnosis of HypoPP. The proband had no history of typical generalized periodic weakness. Physical examination revealed a proximal myopathy evaluated at 3/5 on the medical research council (MRC) scale. He did not show any facial or bulbar weakness. Forced vital capacity was 89%. He did not show any joint contractures. He did not present any percussion nor electrical myotonia. Electromyography of proximal and distal muscles of the 4 limbs showed rare myogenic potentials. There was no evidence of loss of amplitude on the long-effort test. Magnetic resonance imaging (MRI) of lower limbs showed a major fatty replacement of the thigh muscles with a partial sparing of the *adductor* muscle, the *rectus femoris* and the *gracilis* muscles and a complete fatty replacement of the *psoas* muscles at the pelvis (Fig. 2 and 3). A moderate elevated serum CK-level was found (value at last visit: 1826 U/L; normal range 39–308). Muscle biopsy of the left biceps was sampled at the age of 68 and showed numerous atrophic fibers

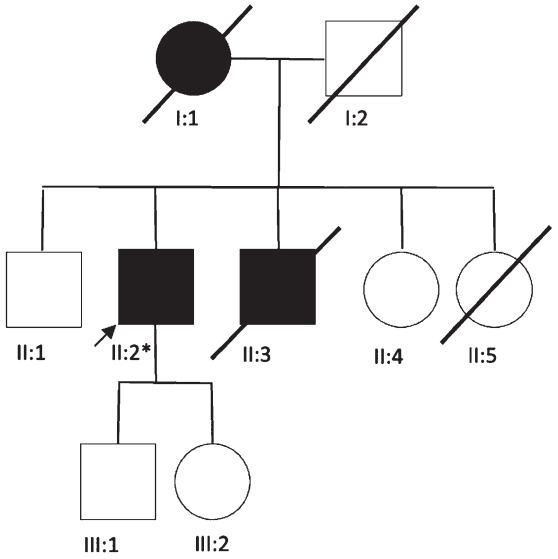

Fig. 1. Family tree. *p.R528H (c.1583G>A).

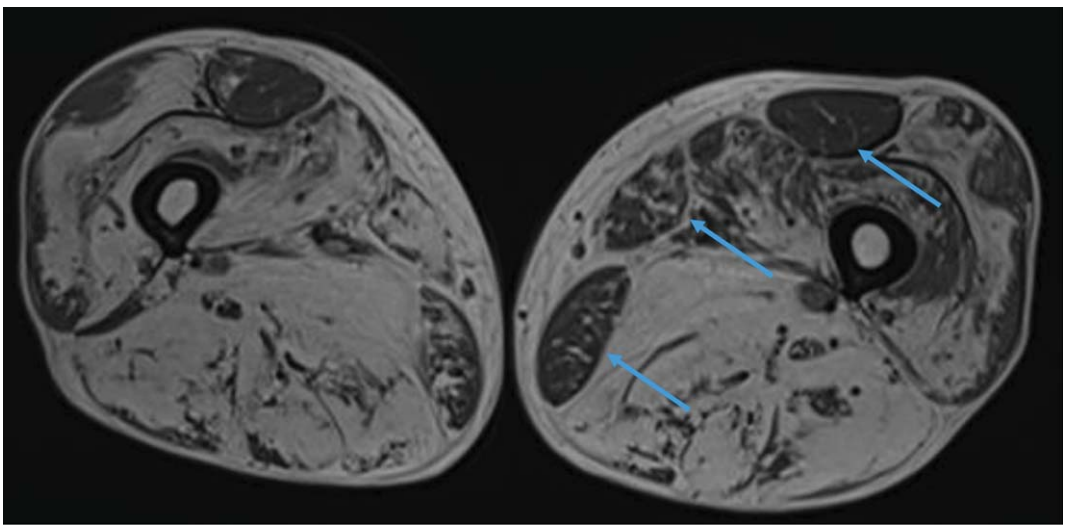

Fig. 2. Lower limb MRI. Major fatty replacement of the thigh muscles with partial sparing of the adductor muscle, the *rectus femoris* and the gracilis muscles (arrows).

with many vacuoles containing tubular aggregates (Fig.4). Myosin ATPase staining showed a normal fiber-type distribution. The proband's brother (PII.3) experienced paralytic attacks from the age of 27. He was evaluated when aged 39 and clinical examination (beyond the paralytic episodes) was reported as normal. Intravenous glucose administration did not provoke conclusive results. Muscle biopsy (left deltoid) showed moderate-to-severe vacuolar changes with rare tubular aggregates. No further medical information was available. He died at the age of 72. Exome-sequencing was performed on the proband and data were filtered according to a list of 548 genes involved in neuromuscular diseases. The common pathogenic p.R528H mutation in the *CACNA1S* gene

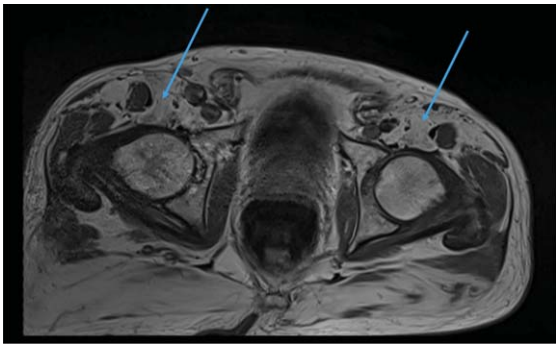

Fig. 3. MRI of the pelvis. Complete fatty replacement of the psoas muscles (arrows).

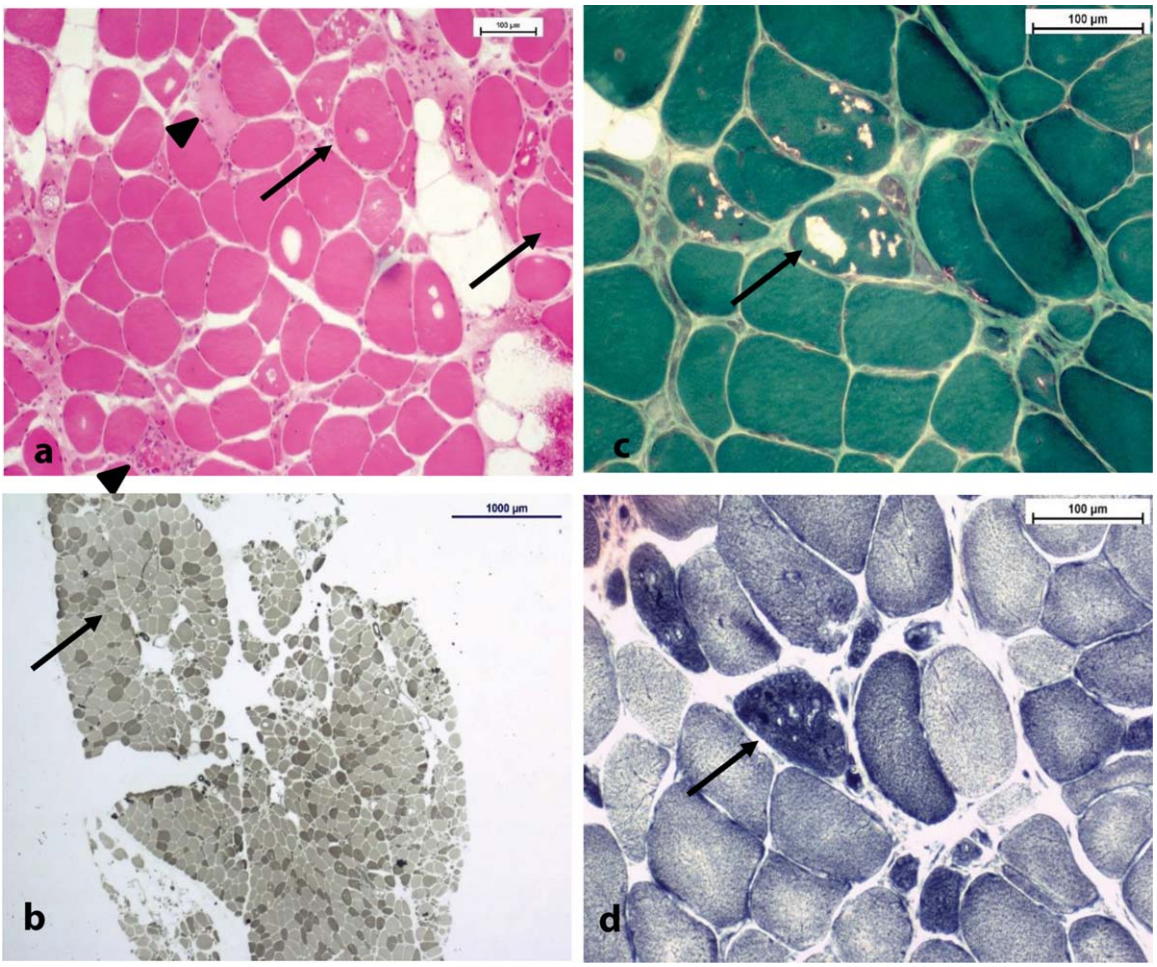

Fig. 4. (**a**) H& E stain x10; note the internalized nuclei (arrows), necrotic fibers (spike arrows) and the numerous atrophic fibers (non-indicated) bars = 100µm. (**b**) ATPase pH 9,4 stain x2; normal fiber-type distribution, as Type II atrophic fibers can be spotted (arrow); bars = 1000μm. Type I predominance. (**c,d**) Same spot in Gömöri trichrome stain (c) and NADH (d) stain x20, respectively; note the variable aspect of vacuoles (arrow) in each stain. Tubular aggregates have a dark staining pattern in NADH ((d) - arrow) despite the aspect of vacuoles (+/- rimmed) in Gömöri trichrome stain ((c) - arrow) bars = 100µm.

was identified in a heterozygote state and was confirmed by Sanger sequencing. DNA from other family members was not available. This mutation has been commonly reported in affected individuals from different families with HypoPP [4, 9, 10]. Contrastingly, our patient did not present episodic paralysis and early-onset myopathy was the sole manifestation.

DISCUSSION

Primary hypokalemic periodic paralysis (HypoPP) typically presents before the age of 20 with transient attacks of muscle weakness. Severity and duration of the episodes vary, lasting from hours to days [9]. Paralytic attacks are usually precipitated by carbohydrate-rich meals, rest after exercise and stress-related illness; all are conditions that favor the entry of potassium into cells. The HypoPP phenotype classically involves normal muscle-strength between paralytic episodes. Some patients may however develop a permanent muscle-weakness over time, generally after the fourth decade, whereby paralytic attacks decrease in frequency [10]. The association between periodic paralysis and permanent muscle weakness has long fueled debates, since the relationship between the frequency and severity of previous attacks and the myopathy has not been well-established. It is thought that weakness might be the result of a more complex process than just the damage accumulated by repetitive attacks [11]. Pathologically, HypoPP-related myopathy is characterized by the presence in muscle fibers of vacuoles containing granular material and abnormal dilatation of the sarcoplasmic reticulum [12]. Vacuolar changes, though non-pathognomonic, are considered as the histological hallmark of HypoPP and can be found at disease-onset. Links et al. stated in 1990 that vacuolar changes were the *primum movens* of a myopathy unrelated to paralysis attacks [11]. Many authors nowadays agree with this statement [8]. Concerning the distribution of weakness, HypoPP related myopathy shows both a proximal and distal involvement, mainly involving the lower limbs. Our patient presented a major, symmetrical involvement of the posterior compartment of the thighs and a sparing of *rectus femoris* and *gracilis* as depicted in previous observations [8]. In the family we are reporting here, the phenotypic expression in the different family members was heterogeneous: in the proband, the myopathy was early-onset and with no PP. The two other affected family-members however seemingly presented HypoPP based on their clinical history. It is noteworthy that the p.R528H mutation was previously identified in a large family as causing HypoPP and a late-onset myopathy without paralytic attacks [13]. These findings were further confirmed in a more recent, large cohort study on the *CACNA1S* mutations spectrum [8]. Our case additionally highlights the intra-familial phenotypic variability of *CACNA1S* gene mutation and related HypoPP. The question of what determines this pronounced intra-familial variability remains open and should be investigated in future studies. In summary, the proband in this affected family presented with an early-onset myopathy evolving since the age of 35. *CACNA1S*-related pathogenic mutation can rarely present with a purely myopathic phenotype. To the best of our knowledge, this had been previously reported in only 7 patients, and never with a clinical onset younger than the age of 35 [8, 13, 14]. Our report on this progressive early-onset myopathy associated with a heterozygous *CACNA1S* mutation expands the phenotypical spectrum of *CACNA1S*-related muscle diseases and should imply considering it in the differential diagnosis of younger adult-onset myopathies especially when featuring myopathies with tubular aggregates.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

REFERENCES

[1] Jurkat-Rott K, Lehmann-Horn F, Elbaz A, Heine R, Gregg RG, Hogan K et al. A calcium channel mutation causing hypokalemic periodic paralysis. Hum Mol Genet. 1994;3(8):1415-9. doi: 10.1093/hmg/3.8.1415. PMID: 7987325.

[2] Rüdel R, Lehmann-Horn F, Ricker K, Küther G. Hypokalemic periodic paralysis: *in vitro* investigation of muscle fiber membrane parameters. Muscle Nerve. 1984;7(2):110-20. doi: 10.1002/mus.880070205. PMID: 6325904.

[3] Elbaz A, Vale-Santos J, Jurkat-Rott K, Lapie P, Ophoff RA, Bady B et al. Hypokalemic periodic paralysis and the dihydropyridine receptor (CACNL1A3): genotype/phenotype correlations for two predominant mutations and evidence for the absence of a founder effect in 16 caucasian families. Am J Hum Genet. 1995;56(2):374-80. PMID: 7847370; PMCID: PMC1801148.

[4] Jurkat-Rott K, Weber MA, Fauler M, Guo XH, Holzherr BD, Paczulla A et al. K+-dependent paradoxical membrane depolarization and Na+ overload, major and reversible contributors to weakness by ion channel leaks. Proc Natl Acad Sci U S A. 2009;106(10):4036-41. doi: 10.1073/pnas.0811277106. Epub 2009 Feb 18. PMID: 19225109; PMCID: PMC2644652.

[5] Ptácek LJ, Tawil R, Griggs RC, Engel AG, Layzer RB, Kwieciński H, et al. Dihydropyridine receptor mutations cause hypokalemic periodic paralysis. Cell. 1994;77(6):863-8. doi: 10.1016/0092-8674(94)90135-x. PMID: 8004673.

[6] Monnier N, Procaccio V, Stieglitz P, Lunardi J. Malignant-hyperthermia susceptibility is associated with a mutation of the alpha 1-subunit of the human dihydropyridine-sensitive L-type voltage-dependent calcium-channel receptor in skeletal muscle. Am J Hum Genet. 1997;60(6):1316-25. doi: 10.1086/515454. PMID: 9199552; PMCID: PMC1716149.

[7] Schartner V, Romero NB, Donkervoort S, Treves S, Munot P, Pierson TM et al. Dihydropyridine receptor (DHPR, CACNA1S) congenital myopathy. Acta Neuropathol. 2017;133(4):517-33. doi: 10.1007/s00401-016-1656-8. Epub 2016 Dec 23. PMID: 28012042.

[8] Holm-Yildiz S, Witting N, Dahlqvist J, de Stricker Borch J, Solheim T, Fornander F et al. Permanent muscle weakness in hypokalemic periodic paralysis. Neurology. 2020;95(4):e342-e352. doi: 10.1212/WNL.0000000000009828. Epub 2020 Jun 24. PMID: 32580975.

[9] Fouad G, Dalakas M, Servidei S, Mendell JR, Van den Bergh P, Angelini et al. Genotype-phenotype correlations of DHP receptor alpha 1-subunit gene mutations causing hypokalemic periodic paralysis. Neuromuscul Disord. 1997;7(1):33-8. doi: 10.1016/s0960-8966(96)00401-4. PMID: 9132138.

[10] Miller TM, Dias da Silva MR, Miller HA, Kwiecinski H, Mendell JR, Tawil R et al. Correlating phenotype and genotype in the periodic paralyses. Neurology. 2004;63(9):1647-55. doi: 10.1212/01.wnl.0000143383.91137.00. PMID: 15534250.

[11] Links TP, Zwarts MJ, Wilmink JT, Molenaar WM, Oosterhuis HJ. Permanent muscle weakness in familial hypokalaemic periodic paralysis. Clinical, radiological and pathological aspects. Brain. 1990;113(6):1873-89. doi: 10.1093/brain/113.6.1873. PMID: 2276049.

[12] Gold R, Reichmann H. Muscle pathology correlates with permanent weakness in hypokalemic periodic paralysis: a case report. Acta Neuropathol. 1992;84(2):202-6. doi: 10.1007/BF00311396. PMID: 1381862.

[13] Chalissery AJ, Munteanu T, Langan Y, Brett F, Redmond J. Diverse phenotype of hypokalaemic periodic paralysis within a family. Pract Neurol. 2018;18(1):60-65. doi: 10.1136/practneurol-2017-001677. Epub 2017 Sep 28. PMID: 28972032.

[14] Sternberg D, Maisonobe T, Jurkat-Rott K, Nicole S, Launay E, Chauveau D, et al. Hypokalaemic periodic paralysis type 2 caused by mutations at codon 672 in the muscle sodium channel gene SCN4A. Brain. 2001;124(Pt 6):1091-9. doi: 10.1093/brain/124.6.1091. PMID: 11353725.