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# SUDDEN TETRAPLEGIA FROM HYPOKALAEMIC PERIODIC PARALYSIS DUE TO CACNA1S MUTATION: SHOULD GENETIC TESTING BE PERFORMED MORE OFTEN?

Simon Bedenbender[1], Jonas Einloft[1], Philipp Russ[1,2], Hendrik Leif Meyer[1], Jürgen R. Schaefer[3], Joachim Hoyer[1], Ivica Grgic[1,2]

[1] Department of Internal Medicine and Nephrology, University Hospital Giessen and Marburg, Marburg University, Marburg, Germany
[2] Institute for Artificial Intelligence in Medicine, University Hospital Giessen and Marburg, Marburg University, Marburg, Germany
[3] Center for Undiagnosed and Rare Diseases (ZusE), University Hospital Giessen and Marburg, Marburg University, Marburg, Germany

**Corresponding author's e-mail:** grgic@staff.uni-marburg.de

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## ABSTRACT

*Background:* Paresis and paralysis are often alarming symptoms of a stroke or spinal cord injury and are typically associated with neurological disorders. However, several rare conditions, including myopathies and neuropathies, can also cause paralysis. Due to their low incidence, these diseases are often overlooked, resulting in prolonged diagnostic delays and delayed treatment.

*Case presentation:* Here, we present the case of a 26-year-old German Caucasian male carpenter who was admitted to the neurological emergency department with acute tetraplegia. On admission, his potassium level was critically low but returned to normal levels after oral potassium supplementation. He was discharged symptom-free with a diagnosis of hypokalaemic paralysis of unclear origin. However, after he experienced a second episode approximately 1.5 years later, we performed genetic analysis and identified an R528H *CACNA1S* mutation as the underlying cause of hypokalaemic periodic paralysis. Further genealogical testing revealed that his asymptomatic mother and maternal grandmother were the carriers of the mutation. A decade after his initial presentation, the patient continues to manage episodes of muscle weakness effectively with oral potassium supplementation, avoiding hospitalization.

*Conclusion:* This case highlights the importance of considering rare diseases in the differential diagnosis when common causes remain unconfirmed, emphasizing the need for timely genetic testing to facilitate an early precise diagnosis and appropriate management.

## KEYWORDS

Hypokalaemic periodic paralysis (HypoPP), electrolyte imbalance, hereditary channelopathy, rare disease, *CACNA1S* mutation

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## LEARNING POINTS

- *CACNA1S* mutations should be considered in patients with recurrent episodes of muscle weakness or paralysis accompanied by hypokalaemia, especially if there is a family history of similar symptoms.

## INTRODUCTION

Paresis and paralysis are often alarming symptoms of a stroke or spinal cord injury and are typically linked to neurological disorders[1]. However, several rare diseases, including myopathies and neuropathies, can also cause paralysis[2]. Due to their low incidence, these conditions are often overlooked, leading to delayed diagnosis and treatment in affected patients. To raise awareness among clinicians, we present the intriguing case of an otherwise healthy 26-year-old male with sudden-onset tetraplegia, in whom genetic analysis identified an R528H *CACNA1S* mutation as the cause of hypokalaemic periodic paralysis.

## CASE DESCRIPTION

A 26-year-old German Caucasian male was admitted to the neurological emergency department by emergency medical services with sudden-onset tetraplegia. He was conscious, alert, and oriented to person, place, and time. Cranial nerves, swallowing, and breathing were unaffected. On admission, his potassium level was critically low at 2.8 mEq/l, with elevated urinary potassium excretion (180 mEq/day). Oral potassium supplementation (potassium citrate tablets) restored potassium levels to normal *(Table 1)*. Additionally, elevated creatine kinase (CK) levels were detected without a proportional rise in creatine kinase muscle/brain (CK-MB), and this abnormality normalized rapidly upon potassium supplementation. The patient denied drug use or recent episodes of diarrhoea or vomiting. Thyroid-stimulating hormone (TSH), free triiodothyronine (T3) and free thyroxine (T4) were within the physiological range, without any indication of thyroid dysfunction.

Neurological examination at the time of admission revealed significant muscle weakness, which spontaneously improved by the end of the first day of hospitalization. Electromyography (EMG) and nerve conduction velocity (NCV) performed on day 6 showed no evidence of peripheral neuropathy, myopathy, or myasthenia. Magnetic resonance imaging of the central nervous system ruled out acute

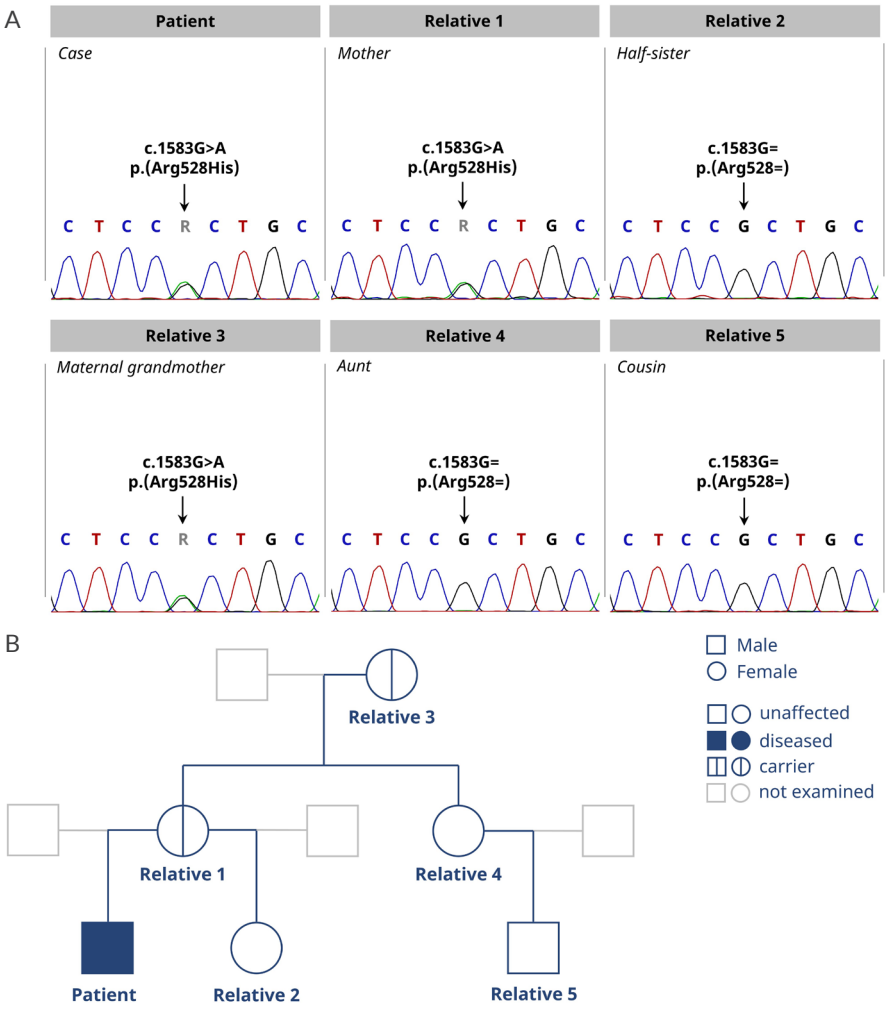



*Figure 1. Genetic analysis. A) Sanger sequencing results for the patient and five relatives, demonstrating the presence or absence of the R528H mutation in CACNA1S. B) Genealogical tree illustrating family relationships and the CACNA1S (R528H) test results for the individuals examined.*

ischemia, inflammation, or haemorrhage. Cerebrospinal fluid (CSF) analysis was unremarkable, providing no indication of an underlying central nervous system disorder. Additionally, microbiological and virological tests in both blood and CSF showed no signs of acute infection. Autoimmune testing was also negative. No further paralytic episodes occurred during hospitalization. After 14 days, the patient was discharged with a diagnosis of hypokalaemic paralysis of unclear origin.

A year and a half later, the patient was readmitted following a sudden and severe recurrence of symptoms. During the night, he experienced mild paralytic symptoms but returned to sleep after taking a potassium tablet, following a day of celebrating his birthday and consuming a large pizza, cake, and drinks. By morning, he was completely unable to move. Upon arrival at the emergency department, he was found to have a complete loss of voluntary motor strength in all four limbs (grade 0/5), accompanied by areflexia. Shortly after admission, he regained minimal movement in his arms and legs (grade 1/5) but was able to move his head. Cranial nerve function appeared intact. A general

| | | First event | | | | Second event | | |
|---|---|---|---|---|---|---|---|---|
| | Reference range | At admission | 1st day after admission | 6th day after admission | 13th day after admission | At admission | 2nd day after admission | 3rd day after admission |
| Sodium (mEq/l) | 136-140 | 143 | 140 | 141 | 140 | 144 | 138 | 134 - |
| Potassium (mEq/l) | 3.6-4.8 | 2.8 - | 4.1 | 3.9 | 4.2 | 2.3 - | 4.6 | 4.3 |
| Calcium (mEq/l) | 1-1.35 | 1.1 | 1.1 | 1.2 | 1.2 | 1.2 | 1.15 | 1.15 |
| AST (U/l) | <35 | 67 + | 89 + | 22 | 17 | 20 | - | - |
| ALT (U/l) | <45 | 38 | 39 | 38 | 27 | 26 | - | - |
| ALP (U/l) | 38-126 | 74 | 68 | 23 | | 95 | - | - |
| GGT (U/l) | <55 | 20 | 15 | 254 + | 25 | 21 | - | |
| LDH (U/l) | <248 | 246 | 276 + | - | - | 236 | 172 | 180 |
| CK (U/l) | <171 | | 2531 + | - | - | 255 + | 757 + | 459 + |
| Bilirubin, total (mg/dl) | 0.3-1.2 | 0.5 | 0.6 | - | - | 0.5 | - | - |
| Glucose (mg/dl) | 74-106 | 96 | 83 | 91 | 100 | 120 + | 96 | 94 |
| Protein (mg/dl) | 61-79 | 68 | 67 | 76 | 75 | 82 + | 67 | 71 |
| Creatinine (mg/dl) | 0.7-1.2 | 0.87 | 0.68 - | 0.81 | 0.84 | 0.76 | 0.79 | 0.8 |
| GFR, MDRD (ml/min/1.73 $m^2$) | 80-140 | 106 | > 140 + | 115 | 110 | 123 | 118 | 116 |
| BUN (mg/dl) | 17-43 | 12.6 | 11.2 | 15.4 | 14.5 | 14 | 5.6 | 12.1 |
| Leukocytes (×$10^3$/µl) | 3.9-10.2 | 15.2 + | 11.1 + | 8.59 | 10.3 + | 9.36 | 7.89 | 8.16 |
| C-reactive protein (mg/dl) | <5 | <0.5 | 0.7 + | <0.5 | 1.1 + | <0.5 | <0.5 | <0.5 |
| Erythrocytes (×$10^6$/µl) | 4.3-5.75 | 5.4 | 5.5 | 5.6 | 5.6 | 6.1 + | 5.9 + | 6.1 + |
| Hemoglobin (g/dl) | 135-172 | 15.8 | 16 | 16.3 | 16.4 | 17.8 + | 17 | 17.6 + |
| Hematocrit | 0.4-0.51 | 0.45 | 0.45 | 0.47 | 0.46 | 0.51 | 0.48 | 0.49 |
| MCV (fl) | 80-99 | 84 | 82 | 85 | 83 | 83 | 81 | 80 |
| MCH (pg) | 27.0-33.5 | 29 | 29 | 29 | 30 | 29 | 29 | 29 |
| MCHC (g/l) | 315-360 | 348 | 355 | 345 | 357 | 352 | 256 | 361 + |
| Thrombocytes (×$10^3$/µl) | 150-370 | 217 | 222 | 234 | 245 | 249 | 218 | 236 |

**Note:** Conversion factors for units: calcium in mEq/l to mmol/l, ×0.5; bilirubin in mg/dl to µmol/l, ×17.1; glucose in mg/dl to mmol/l, ×0.0555; creatinine in mg/dl to µmol/l, ×88.4; BUN in mg/dl to mmol/l, ×0.357.

**Abbreviations:** ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; GFR, glomerular filtration rate; MDRD, modification of diet in renal disease; GGT, gamma-glutamyl transferase; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; LDH, lactate dehydrogenase; BUN, blood urea nitrogen. Plus (+) and minus symbols (-) indicate an increase or decrease of values relative to the reference range, respectively.

*Table 1. Laboratory results.*

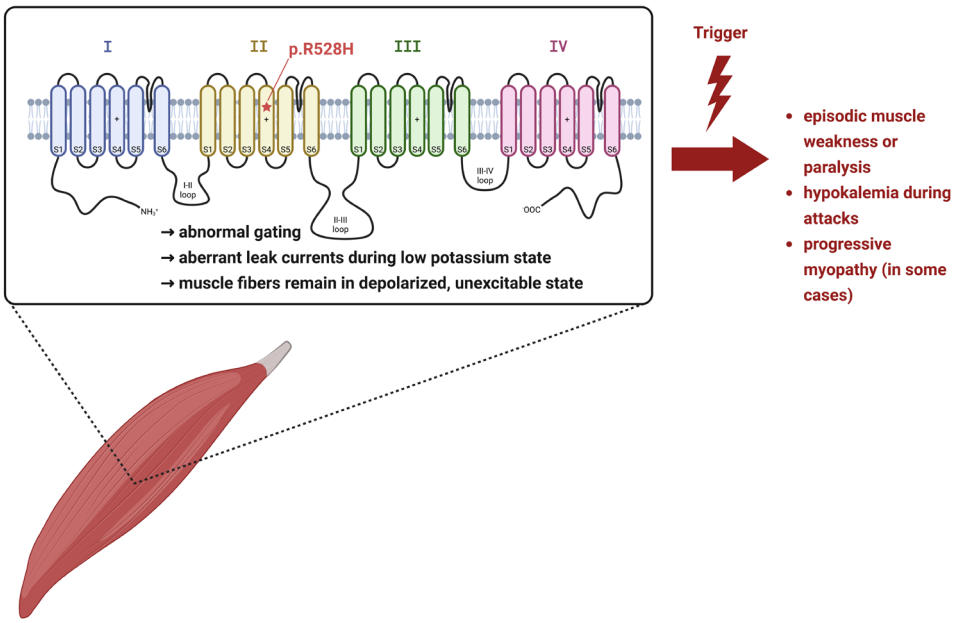



*Figure 2. Simplified illustration of the pathomechanism of CACNA1S mutation (R528H)–associated hypokalaemic periodic paralysis. Triggers (e.g., high-carbohydrate load, rest after physical exertion, alcohol) promote an intracellular $K^+$ shift, leading to a low-potassium state and precipitating episodic weakness/paralysis in susceptible individuals. Pathogenic variants such as CACNA1S R528H in the S4 voltage sensor of the CaV1.1 channel create an aberrant "gating-pore" leak current, producing a paradoxical depolarization of the resting membrane potential and rendering skeletal muscle fibres unexcitable. Positively charged, arginine-rich S4 segments are marked with "+". Created with BioRender.*

physical examination revealed a moderately reduced overall condition, although the patient remained alert and oriented to person, place, and time. Cardiovascular and abdominal examinations were unremarkable. Peripheral perfusion was adequate, with warm extremities and no evidence of oedema. The patient reported a smoking history of 8–10 pack-years and occasional alcohol consumption but denied illicit drug use. He also stated that he usually took only one potassium tablet per week. Laboratory evaluation revealed a potassium level of 2.3 mEq/l, consistent with a recurrent episode of hypokalaemic paralysis. Gradual oral potassium supplementation was initiated, resulting in a marked improvement in motor function on the same day *(Table 1)*. Concomitant elevated levels of CK were again observed but normalized following potassium repletion. The patient quickly regained full strength, and no further paralytic episodes occurred during his hospital stay. The working diagnosis of hypokalaemic periodic paralysis (HypoPP) was substantiated, prompting genetic testing for definitive confirmation.

Consequently, we conducted a genetic analysis of the *CACNA1S* and *SCN4A* genes, which account for ~70% of HypoPP cases[3]. Genomic DNA was extracted from peripheral leukocytes, and the exons of interest of both genes were selectively amplified using primer-directed polymerase chain reaction (PCR). The purified amplicons were analysed via Sanger sequencing. The results were mapped against the reference sequence of *CACNA1S* and *SCN4A*, and variants were called using Geneious Prime. Detailed methods are provided in the *Appendix*, with information on amplified exons and primers, as well as the PCR conditions.

Sanger sequencing results revealed a well-known pathogenic R528H mutation within exon 11 of the *CACNA1S* gene *(Fig. 1A)*, which is associated with HypoPP[4-6]. The chromatogram confirmed heterozygosity, displaying peaks for both the reference base adenine (A) and the mutant base guanine (G). This was further supported by a variant allele frequency of 50%, as calculated by the variant caller. Interestingly, the patient had no known family history of symptomatic hypokalaemia, paralysis, or, specifically, hypokalaemic periodic paralysis. To understand the inheritance pattern, we analysed the patient's close family members *(Fig. 1A)*, allowing the construction of a genealogical tree *(Fig. 1B)*. Unexpectedly, we identified the mutation in the patient's mother and maternal grandmother. Notably, his maternal half-sister tested negative for the mutation, as did his maternal aunt and her son. However, both his mother and grandmother had never experienced signs of hypokalaemia or paralysis, suggesting they were asymptomatic carriers of the mutation.

After three days of hospitalization, the patient was discharged symptom-free. He was advised to avoid a high-carbohydrate diet, intense physical exertion, and prolonged exposure to cold (*Fig. 2*). Additionally, he was prescribed oral potassium supplementation for prophylaxis and educated on potassium-rich food sources.

At 10-year follow-up, the patient reported experiencing several episodes of mild muscle weakness in the first three to four years after his second hospital stay, all of which resolved quickly with oral potassium supplementation and did not require hospitalization. Of note, he did vividly recall one episode of significant muscle weakness following an intramuscular cortisone injection for back pain, but symptoms subsided within hours after taking additional

potassium tablets. Initially, he adhered to daily oral potassium supplementation but later took it only when signs of muscle weakness emerged. In the last three years, he completely discontinued potassium tablets without any recurrence of symptoms. However, he maintained a regular intake of bananas and adhered to a low-carb diet. There was no evidence of muscle atrophy or strength decline; rather, he showed increased muscle mass due to regular exercise.

## DISCUSSION

Here, we present the instructive case of a 26-year-old male with sudden-onset tetraplegia, ultimately diagnosed with hypokalaemic periodic paralysis (HypoPP) caused by an R528H mutation in the *CACNA1S* gene.

The *CACNA1S* gene encodes the pore-forming alpha-1S subunit of the voltage-gated calcium channel Cav1.1, also known as the dihydropyridine receptor. This channel plays a crucial role in excitation-contraction coupling in skeletal muscle by interacting with the ryanodine receptor (RyR1). Mutations in *CACNA1S* and a second gene, *SCN4A*, which encodes the pore-forming subunit of the voltage-gated sodium channel Nav1.4, are the primary causes of HypoPP, a rare genetic disorder with an estimated prevalence of 1:100,000[7,8]. The majority of mutations are found in *CACNA1S* accounting for approximately 60-70% of cases[3,7], with arginine substitutions in the voltage-sensing domain of *CACNA1S* or *SCN4A* accounting for nearly 90% of all known mutations. The R528H variant identified in our patient is among the most commonly reported mutations[4-6]. Importantly, several other *CACNA1S* variants have also been associated with malignant hyperthermia – a rare but potentially life-threatening anaesthetic reaction – although this association has not been reported for R528H.

Triggers of HypoPP episodes typically include strenuous exercise and high-carbohydrate meals[8]. Notably, our patient experienced a second severe episode after celebrating and consuming large amounts of pizza and cake. Interestingly, he also reported muscle weakness following a corticosteroid injection, a less commonly recognized but documented trigger of HypoPP[3].

Family history analysis revealed that both his mother and maternal grandmother were carriers of the R528H mutation, yet neither had ever exhibited symptoms of hypokalaemia or periodic paralysis. This observation aligns with prior research indicating incomplete penetrance of R528H among female carriers, with males more frequently affected than females[5,8,9]. Furthermore, age at onset varies by mutation. For instance, the R528H mutation has been reported to manifest at 14.5 ± 1.5 years[9] or, in other reports, 14 ± 5 years[5], whereas in our case, symptoms first appeared at age 26, slightly later than expected. However, the possibility of mild, undiagnosed episodes in childhood or adolescence cannot be entirely ruled out.

During a 10-year follow-up period after his second hospital admission, the patient experienced only one additional episode of significant muscle weakness, which did not require hospitalization. This aligns with the literature describing a broad range of attack frequencies, varying from several per week to only one episode in a lifetime[3]. In terms of long-term management, patients with HypoPP benefit from oral potassium supplementation and avoidance of triggers, including excessive exercise, stress, and high-carbohydrate intake[10]. In this case, adherence to these preventive strategies successfully alleviated symptoms and prevented more severe attacks.

In conclusion, we report a case of HypoPP caused by a *CACNA1S* mutation, a rare but important differential diagnosis for paralysis. This case underscores the need for clinicians to consider rare diseases, including channelopathies, when common causes remain unconfirmed. Although not reported for R528H, several other *CACNA1S* variants have been associated with malignant hyperthermia susceptibility; accordingly, targeted genetic testing in suspected cases is increasingly valuable, with the potential to prevent catastrophic complications by informing diagnosis and counselling and enabling proactive peri-anaesthetic risk mitigation. Advances in artificial intelligence and diagnostic technologies may further enhance the early identification of rare diseases, ultimately improving patient care and outcomes.

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## APPENDIX

*Genomic DNA isolation and PCR amplification*

For isolation of genomic DNA (gDNA), leukocytes were separated from 5 ml of whole EDTA blood by centrifugation for 10 min at 2,500 × *g* and resuspended in 200 µl Dulbecco's phosphate-buffered saline (DPBS, Thermo Scientific). Subsequently, genomic DNA was isolated from the separated leukocytes using the QIAamp DNA Mini kit (QIAGEN) according to the manufacturer's protocol for DNA Purification from Blood or Body Fluids (Spin Protocol). Purified gDNA was used as template for specific amplification of the sequences of interest *(see Table 1 and 2)* via PCR. PCR reactions were performed in 25 µl reactions containing 0.25 µl peqGOLD Taq DNA polymerase (Peqlab), 2.5 µl 10x reaction buffer Y, 800 µM dNTP mix (Thermo Scientific), 0.2 µM of each forward and reverse primer and 50 ng genomic DNA. PCR conditions were optimized for each amplicon individually *(Table 3)*. Purity and correct sizes of the amplicons were verified by DNA agarose gel electrophoresis. Amplicons were cut from the gel and purified using the QIAquick Gel Extraction Kit (QIAGEN) according to the manufacturer's protocol. DNA concentration was determined using the NanoDrop 2000c (Thermo Scientific).

*Sanger sequencing*

Sanger sequencing was performed by Microsynth Seqlab (Göttingen). For this purpose, purified amplicons were used to prepared primer-premixed sequencing reactions as required by the manufacturer. All sequencing runs were carried out both in forward and in reverse direction to rule out sequencing errors.

*Bioinformatic analysis*

Bioinformatic analysis was performed with Geneious Prime 2025.0.3 (https://www.geneious.com). For analysis of the Sanger sequencing results, chromatograms were imported and mapped against the *CACNA1S* (NG_009816.2) or the *SNC4A* (NG_011699.1) reference sequence using the Geneious mapper with standard settings. Subsequently, variant calling was performed using the implemented Variants/SNPs caller using a minimum variant frequency of 0.25 without calculating variant p-values. To verify called variants as mutations, variants needed to occur in both the forward and reverse sequencing runs.

| Amplicon | Exons covered | Position | Length (bp) | Primer ID | Sequence |
|---|---|---|---|---|---|
| 1 | 11 | 34,024-34,781 | 758 | CACNA_I_fw | ACATGACGAAACCCTGTCTC |
| | | | | CACNA_I_rv | CCTGCCCTGCCATAGACTAT |
| 2 | 20+21 | 45,268-46,342 | 1075 | CACNA_II_fw | GAAATGCATTTAGGCCACTGC |
| | | | | CACNA_II_rv | TACCCCAGCCTCATCCTTAC |
| 3 | 30+31 | 58,741-59,386 | 646 | CACNA_III_fw | CATCTCCCCAAAACACACAGT |
| | | | | CACNA_III_rv | ACTCCAGCCATCCACGATC |

*Table 1. Amplicons and primers used for the Sanger sequencing of CACNA1S.*

| Amplicon | Exons covered | Position | Length (bp) | Primer ID | Sequence |
|---|---|---|---|---|---|
| 1 | 12 | 13,261-13,798 | 538 | SCN4A_12_fw | TCTCAGAGTTGTACCCACCT |
| | | | | SCN4A_12 rv | GGTAACAGGTGTGCACAAGG |
| 2 | 13 | 15,251-15,950 | 700 | SCN4A_13_fw | TCCCATTTAGCAGAAGGGC |
| | | | | SCN4A_13_rv | GCCGGGGATCTATGTTTTAAGT |
| 3 | 18 | 25,633-25,987 | 355 | SCN4A_18_fw | AGGGAGGGGATCTAAGGGAG |
| | | | | SCN4A_18_rv | CTCTCTGCTTCCCTCTGGT |

*Table 2. Amplicons and primers used for the Sanger sequencing of SNC4A.*

| Step | CACNA1S 1 and 3, SCN4A 2 | CACNA1S 2 | SCN4A 1 | SCN4A 3 |
|---|---|---|---|---|
| **Initial denaturation** | 95°C 2:00 min | | | |
| **40 cycles:** | | | | |
| **Denaturation** | 95°C 00:15 | 95°C 00:15 | 95°C 00:15 | 95°C 00:15 |
| **Annealing** | 58°C 00:15 | 58°C 00:15 | 60°C 00:15 | 64°C 00:15 |
| **Elongation** | 68°C 00:45 | 68°C 01:10 | 68°C 00:45 | 68°C 00:30 |
| **Final elongation** | 68°C 5:00 min | | | |

*Table 3. PCR conditions for the six amplicons.*