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Case Report

# X-linked Charcot–Marie–Tooth disease type 5 with recurrent weakness after febrile illness

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**Abstract**

X-linked Charcot–Marie–Tooth disease type 5 (CMTX5) is an X-linked disorder characterized by early-onset sensorineural hearing impairment, peripheral neuropathy, and progressive optic atrophy. It is caused by a loss-of-function mutation in the phosphoribosyl pyrophosphate synthetase 1 gene (*PRPS1*), which encodes isoform I of phosphoribosyl pyrophosphate synthetase (PRS-I). A decreased activity leads to nonsyndromic sensorineural deafness (DFN2), CMTX5, and Arts syndrome depending upon residual PRS-I activity. Clinical and neurophysiological features of pediatric CMTX5 are poorly defined. We report two male siblings with peripheral neuropathy and prelingual sensorineural hearing loss who carried a novel c.319A>G (p.Ile107Val) *PRPS1* missense mutation. They exhibited recurrent episodes of transient proximal muscle weakness, showing Gowers' sign and waddling gait after suffering from febrile illness. This transient weakness has not been previously reported in CMTX5. A patient with Arts syndrome was reported to have transient proximal weakness after febrile illness. The transient weakness presenting in both CMTX5 and Arts syndrome suggests an overlap of signs and a continuous spectrum of PRS-I hypoactivity disease. Children presenting with transient neurological signs should be evaluated for peripheral neuropathy and consider genetic analysis for *PRPS1*.


*Keywords:* Charcot–Marie–Tooth disease; PRPS1 gene; Hearing impairment; Acute weakness

## 1. Introduction

X-linked Charcot–Marie–Tooth disease type 5 (CMTX5) is characterized by early-onset sensorineural hearing impairment, peripheral neuropathy, and progressive optic atrophy [1]. CMTX5 is caused by a loss-of-function mutation in phosphoribosyl pyrophosphate synthetase 1 gene (*PRPS1*), which encodes isoform I of phosphoribosyl pyrophosphate synthetase (PRS-I: EC 2.7.6.1) [1]. Three allelic disorders have been described. One is PRPS-related gout (300661) that results from increased PRPS1 enzyme activity [2]. Others are Arts syndrome and X-linked nonsyndromic sensorineural deafness (DFN2), and both are caused by decreased activity of PRS-I and the severity of these disorders depends on the enzyme activity. Arts syndrome is the severest phenotype, presenting with intellectual disability, early-onset hypotonia, ataxia,

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delayed motor development, and immune system impairment [3], and DFN2 shows postlingual progressive hearing loss as an isolated feature. Both diseases and CMTX5 show some overlap [4]. Less than 20 patients were reported to have CMTX5, and they showed some variability. Therefore, accumulation of the patients is important. We report the cases of two male siblings with CMTX5 involving a novel *PRPS1* mutation who presented with recurrent weakness after febrile illnesses.

## 2. Case report

Patient 1 (subject III-1; Fig. 1) is a 13-year-old male from non-consanguineous Japanese parents with prelingual hearing loss since birth. He had experienced three recurrent, sudden-onset episodes of muscle weakness between 8 and 11 years of age following an upper respiratory tract infection. Neurological evaluation revealed decreased knee and ankle reflexes and severe proximal muscle weakness presenting as Gowers' sign and waddling gait during these episodes. Serum creatine kinase and uric acid levels were 77 IU/L and 4.0 mg/dL, respectively. Clinical recovery occurred within 1 month of onset. A nerve conduction study (NCS) at 12 years of age (Table 1) showed reduced amplitude of the distal compound muscle action potentials (CMAP) in the lower extremities. His examination at 13 years of age showed impaired walking on heels, flat foot, hyporeflexia, and hearing loss.

Patient 2 (subject III-2; Fig. 1), the younger brother of patient 1, developed prelingual sensorineural hearing loss during the first year of life. He showed poor exercise performance and was a slow runner. Episodes of gait difficulty that recurred following febrile illnesses since 2 years of age always resolved within 1 month. He consulted us at the age of 8 years, on the following day after the onset of gait difficulties after febrile illnesses. Neurological evaluation revealed decreased knee and ankle reflexes and severe proximal muscle weakness presenting as Gowers' sign and waddling gait. Brain, spine, and muscle magnetic resonance imaging (MRI) showed no abnormalities. Cerebrospinal fluid was normal. Serum creatine kinase and uric acid levels were 49 IU/L and 5.0 mg/dL, respectively. NCS showed decreased CMAP and temporal dispersion of the tibial and fibular nerves (Table 1, early phase). He regained his baseline level of function within 1 month. He could walk normally and run without falling but had difficulty in heel walking with flat foot. Both knee and ankle reflexes were decreased bilaterally. NCS results in the 2 months following the latest episode were not changed from those of the early phase (Table 1, late phase).

After receiving parental written informed consent, genetic analysis of 72 peripheral neuropathy-related genes was performed using Sanger sequencing; it revealed a novel c.319A>G hemizygous missense *PRPS1* mutation involving a change in a highly conserved amino acid residue (p.Ile107Val, Fig. 1). In silico, this mutation was predicted to be disease-causing (PolyPhen-2 score, 0.999; SIFT score, 0.001; Mutation transfer score, 29). The protocol of the study was approved by the Ethical Committee of Kagoshima University (Kagoshima, Japan). Consistent with X-linked recessive inheritance, the proband was hemizygous and the mother was heterozygous, confirming the diagnosis of CMTX5. The mother did not have a hearing or neurological deficit at the age of 47.

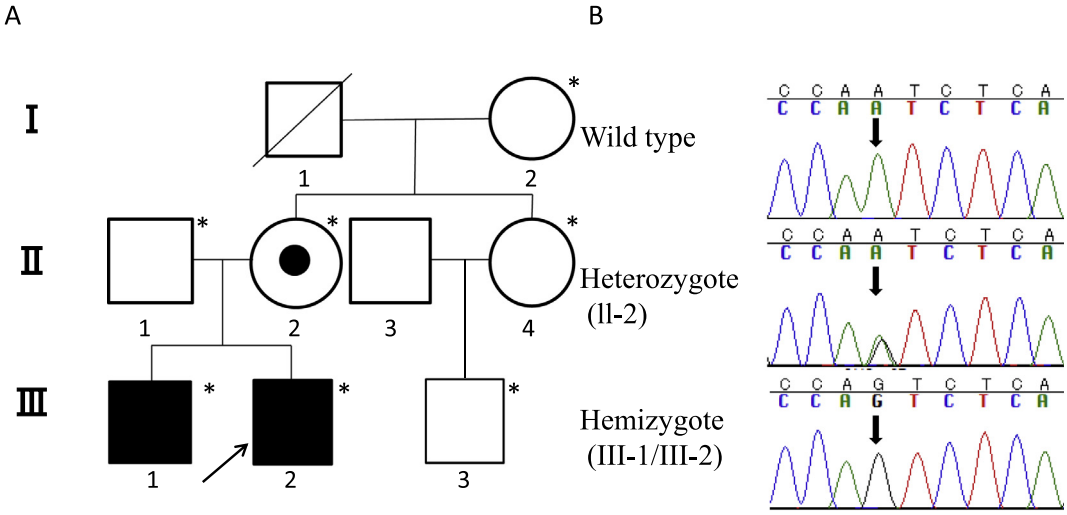


Fig. 1. A: Family pedigree showing maternal inheritance of the *PRPS1* mutation. Open symbols, unaffected individuals; solid symbols, affected individuals; circles with a central dot, carriers of *PRPS1* mutation; arrow, proband; asterisks, individuals whose blood was drawn for genetic analysis. B: Sequencing chromatograms show the PRPS1 c.319A>G (p.Ile107Val) mutation. The affected proband (III-1/III-2) is hemizygous, whereas his unaffected mother is heterozygous. Vertical arrows indicate the mutation site.

Table 1
Electrophysiological findings of the patients.

| | III-1 | III -2 early phase | III -2 late phase | Normal values* |
|---|---|---|---|---|
| | Patient 1 | Patient 2 | | |
| | | Early phase | Late phase | |
| *Motor nerve conduction study* | | | | |
| *TL (ms)* | | | | |
| Median nerve | 3.6 | ND | 3.8 | 2.6 ± 0.3 |
| Ulnar nerve | 3.5 | ND | 3.2 | 2.3 ± 0.3 |
| Fibular nerve | 6.4 | 6.9 | 7.3 | 3.2 ± 0.7 |
| Tibial nerve | 4.1 | 4.3 | 5.9 | 3.6 ± 1.6 |
| *CV (m/s)* | | | | |
| Median nerve | 47.3 | ND | 39.4 | 57.2 ± 3.7 |
| Ulnar nerve | 58.6 | ND | 47.4 | 58.3 ± 5.7 |
| Fibular nerve | 70.2 | 27.9 | 27.9 | 49.6 ± 3.4 |
| Tibial nerve | 50.4 | 34 | 26.9 | 48.2 ± 2.8 |
| *CMAP (mV)* | | | | |
| Median nerve | 5.8 | ND | 2.1 | 8.8 ± 1.9 |
| Ulnar nerve | 4.2 | ND | 2.3 | 10.3 ± 2.0 |
| Fibular nerve | 2.3 | 0.3 | 0.3 | 7.2 ± 1.6 |
| Tibial nerve | 6.9 | 0.95 | 0.37 | 15.8 ± 1.8 |
| *Sensory nerve conduction study* | | | | |
| CV (m/s) | | | | |
| Median nerve (finger–wrist) | 56.8 | ND | 53 | 43.7 ± 3.4 |
| Ulnar nerve (finger–wrist) | 54.8 | ND | 53 | 43.9 ± 3.9 |
| Sural nerve | 49.6 | ND | 43.9 | 42.8 ± 4.8 |
| *SNAP (μV)* | | | | |
| Median nerve (finger–wrist) | 24.3 | ND | 28.9 | 20.5 ± 3.5 |
| Ulnar nerve (finger–wrist) | 19.2 | ND | 23.4 | 14.3 ± 2.5 |
| Sural nerve | 17.4 | ND | 13.7 | 18.7 ± 4.4 |

TL, terminal latency; CV, conduction velocity; CMAP, compound muscle action potentials; SNAP, sensory nerve action potentials; ND, not detected.
Patient 2 early phase: NCS performed when the patient had severe proximal muscle weakness presenting as Gowers' sign and a waddling gait. Patient 2 late phase: NCS performed 2 months following full recovery.
* Adopted from Ref. [10].

## 3. Discussion

The siblings were diagnosed to have CMTX5 on the basis of the phenotypes such as sensorineural hearing loss and peripheral neuropathy, and *PRPS1* missense mutation. Their weakness was predominant in the distal lower extremities. On NCS, patient 1 showed low CMAP, and patient 2 showed both low CMAP and delayed NCV, and results of the studies of sensory nerve were normal. In CMTX5 patients, both of sensorimotor neuropathy and predominantly motor neuropathy has been reported [5]. As for the type of neuropathy, axonal neuropathy was a main feature, but mild delay of NCV was also reported [6]. Although visual impairment which is one of the predominant features of CMTX5 was not observed, this usually occurs at a later age [1].

The patients experienced transient proximal muscle weakness lasting up to 1 month after febrile illnesses. Proximal muscle weakness usually occurs in patients with myogenic diseases. In the present case study, it was unknown whether the exact mechanism of proximal muscle weakness in our patients was myogenic or neurogenic because electromyography was not performed during muscle weakness periods. Guillain–Barré syndrome and myositis were not considered on the basis of disease progression, normal muscle MRIs, CK and CSF studies, and unchanged NCS in early and late phase. Transient neurogenic proximal weakness was reported in Art syndrome.

Maruyama et al. reported episodes of transient post-infection loss of muscle strength in a boy with Arts syndrome [7]. His proximal muscle weakness recovered gradually, enabling him to stand with support at 24 months of age but he could not walk. Electromyography revealed a reduced interference pattern, indicating neurogenic cause; a muscle biopsy revealed active reinnervation. Recurrent infections temporarily exacerbated his weakness [7]. Susceptibility to infections, especially upper respiratory tract infections, almost invariably results in death of Arts syndrome patients younger than 5 years [8]. Recurrent infections cause worsening of their motor performance that does not return to preexisting levels [8].

The occurrence of PRPS1-related neurological dysfunction may be related to demyelination of neurons,

impaired pyrimidine synthesis, reduced GTP levels in association with the high-energy demand of neuronal cells, and the loss of pyridine nucleotide synthesis [3]. Nucleotide defects may also be considered metabolic aspects of some mitochondrial disorders [9]. The cause of recurrent weakness such as metabolic myopathies or peripheral neuropathies might be owing to the high-energy demand of neuronal cells during infections. The transient weakness presenting clinically at times of metabolic stress may be influenced by nucleotide toxicity due to depletion of NAD and ATP.

The neurological phenotypes of PRPS1-related disorders seem to primarily result from reduced levels of guanosine triphosphate (GTP) and other purine nucleotides, including ATP [3]. *PRPS1* mutations would, thus, presumably reduce energy supply in the brain, muscle, and retina. The transient proximal muscle weakness in our patients with CMTX5 and in an Arts syndrome patient [7] may indicate a continuous spectrum of PRS-I hypoactivity disease signs.

Two siblings with CMTX5 polyneuropathy presented with transient proximal muscle weakness associated with a novel *PRPS1* missense mutation. Thus, children presenting with transient neurological signs should be evaluated for peripheral neuropathy. Genetic analysis for CMTX is advised even without clinical evidence of neuropathy.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.braindev.2018.08.006.

## References

[1] Kim HJ, Sohn KM, Shy ME, Krajewski KM, Hwang M, Park JH, et al. Mutations in PRPS1, which encodes the phosphoribosyl pyrophosphate synthetase enzyme critical for nucleotide biosynthesis, cause hereditary peripheral neuropathy with hearing loss and optic neuropathy (cmtx5). Am J Hum Genet 2007;81:552–8.

[2] Sperling O, Boer P, Persky-Brosh S, Kanarek E, De Vries A. Altered kinetic property of erythrocyte phosphoribosylpsyrophosphate synthetase in excessive purine production. Rev Eur Etud Clin Biol 1972;17:703–6.

[3] de Brouwer AP, van Bokhoven H, Nabuurs SB, Arts WF, Christodoulou J, Duley J. PRPS1 mutations: four distinct syndromes and potential treatment. Am J Hum Genet 2010;86:506–18.

[4] Synofzik M, Müller vom Hagen J, Haack TB, Wilhelm C, Lindig T, Beck-Wödl S, et al. X-linked Charcot-Marie-Tooth disease, Arts syndrome, and prelingual non-syndromic deafness form a disease continuum: evidence from a family with a novel PRPS1 mutation. Orphanet J Rare Dis 2014;9:24.

[5] Robusto M, Fang M, Asselta R, Castorina P, Previtali SC, Caccia S, et al. The expanding spectrum of PRPS1-associated phenotypes: three novel mutations segregating with X-linked hearing loss and mild peripheral neuropathy. Eur J Hum Genet 2015;23:766–73.

[6] Park J, Hyun YS, Kim YJ, Nam SH, Kim SH, Hong YB, et al. Exome sequencing reveals a novel PRPS1 mutation in a family with CMTX5 without optic atrophy. J Clin Neurol 2013;9:283–8.

[7] Maruyama K, Ogaya S, Kurahashi N, Umemura A, Yamada K, Hashiguchi A, et al. Arts syndrome with a novel missense mutation in the PRPS1 gene: a case report. Brain Dev 2016;38:954–8.

[8] Arts WF, Loonen MC, Sengers RC, Slooff JL. X-linked ataxia, weakness, deafness, and loss of vision in early childhood with a fatal course. Ann Neurol 1993;33:535–9.

[9] Duley JA, Christodoulou J, de Brouwer AP. The PRPP synthetase spectrum: what does it demonstrate about nucleotide syndromes? Nucleosides Nucleotides Nucleic Acids 2011;30:1129–39.

[10] Cai F, Zhang J. Study of nerve conduction and late responses in normal Chinese infants, children, and adults. J Child Neurol 1997;12:13–8.