pISSN 1738-6586 / eISSN 2005-5013 / J Clin Neurol 2022;18(2):238-240 / https://doi.org/10.3988/jcn.2022.18.2.238

Wide Phenotypic Spectrum of PNMHH Patients With p.R941L Mutation in *MYH14*

Hye Mi Kwon[a*]
Jin Hee Park[b*]
Ki Wha Chung[b]
Byung-Ok Choi[a,c]

[a]Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[b]Department of Biological Sciences, Kongju National University, Gongju, Korea
[c]Stem Cell & Regenerative Medicine Institute, Samsung Medical Center, Seoul, Korea

Received August 6, 2021
Revised October 13, 2021
Accepted October 13, 2021

Correspondence
Byung-Ok Choi, MD, PhD
Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea
Tel +82-2-3410-1296
Fax +82-2-3410-0052
E-mail bochoi@skku.edu

Ki Wha Chung, PhD
Department of Biological Sciences, Kongju National University, 56 Gongjudaehak-ro, Gongju 32588, Korea
Tel +82-41-850-8506
Fax +82-41-850-0957
E-mail kwchung@kongju.ac.kr

*These authors contributed equally to this work.

Dear Editor,

The MYH14 (MIM 608568) gene encodes a member of the nonmuscle myosin heavy-chain II family that affects cytoskeletal actin and regulate cell motility, polarity, and mitochondrial function.[1] Mutations in *MYH14* have been reported to cause autosomal dominant nonsyndromic deafness 4A (DFNA4A; MIM 600652).[2,3] Our research group first reported the *MYH14* p.R941L mutation in a large autosomal dominant Korean family in 2011 (family ID: FC317).[4] This new type of rare genetic disease was registered in the OMIM database (MIM 614369, https://www.omim.org/) with the abbreviated name of PNMHH to reflect its complex phenotypes of peripheral neuropathy (PN), myopathy, hearing loss (HL), and hoarseness (Ho). The p.R941L mutation has subsequently been reported in two families in the United States of America and Canada.[5,6]

In the present study, we identified a second Korean family (family ID: FC1126) with the same *MYH14* p.R941L mutation (Supplementary Fig. 1 in the online-only Data Supplement). The affected individuals exhibited PN, HL, Ho, and myopathy, with phenotypes similar to those for the previously described Korean PNMHH family.[4] Audiological studies showed bilateral sensorineural HL, with greater impairment at high frequencies (Supplementary Fig. 2 in the online-only Data Supplement). Hoarse voice was present in both affected individuals, but paresis of the vocal cords was not found. The affected individuals exhibited distal leg muscle atrophy. MRI showed abnormal fatty infiltration and muscle atrophy in the lower extremities similar to the findings in the previous Korean family, and sequential muscle involvement according to the disease duration was also observed (Supplementary Fig. 3 in the online-only Data Supplement).[4] Fatty infiltration and atrophy were present in the anterior compartment of the legs in the early stage (Supplementary Fig. 3C in the online-only Data Supplement), while posterior-compartment leg muscles were affected in the late stage (Supplementary Fig. 3D in the online-only Data Supplement).

It is of considerable interest that a wide phenotypic spectrum was revealed by comparing the clinical features among the four PNMHH families (including the present family) (Table 1). As the main phenotypes, PN and HL were observed in all of the families, while myopathy and Ho were only observed in two Korean families. When the PN types were compared in detail, the American family was reported to have distal hereditary motor neuropathy without sensory disturbance,[5] but the other three families exhibited sensory loss, which is consistent with hereditary motor and sensory neuropathy and axonal Charcot-Marie-Tooth disease type 2.[4,6]

While HL was observed in all of the families, the onset age and severity varied between the families and even between individuals within a single family. Approximately half of the affected individuals showed no noticeable HL. HL in the Canadian patients occurred prelingually or with an early onset (age 0–4 years), but the other patients exhibited a broad range of HL onset ages, from preteens to the 60s (Supplementary Fig. 4A in the online-only Data

Table 1. Clinical manifestations of PNMHH patients with the p.R941L mutation in *MYH14*

Patients	Korean 1 (FC1126)		Korean 2 (FC317)	American	Canadian
	III-2	II-2			
No. of patients	1	1	15	11	4
Phenotype	CMT2, HL, Ho, myopathy	CMT2, HL, Ho, myopathy	CMT2, HL, Ho, myopathy	dHMN, HL	CMT2, HL
Age at examination (yr)	25	55	11–52	26–77	23–58
Age at onset (yr)					
Muscle weakness	10	8	5–14	4–23	9–10
HL	23	14	15–40	4–67	0–4
Muscle power (MRC scale)*					
Shoulder abduction	5	5	3 to 5	3- to 5	5
Elbow flexion	5	5	4 to 5	4- to 5	5
Elbow extension	5	5	4+ to 5	4 to 5	4- to 5
Wrist extension	5	4+	4+ to 5	4 to 5	4- to 5
Wrist flexion	4+	4+	4- to 5	4- to 5	4- to 5
Finger extension	4	4	4- to 5	ND	3 to 5
Finger flexion	4–	4	2 to 5	ND	3 to 5
Finger abduction	3	3	2 to 5	4- to 4+	3 to 5-
Hip flexion	4+	4	0 to 5	2 to 5	5
Knee extension	4+	4+	0 to 5	3– to 5	5
Knee flexion	4	4	4- to 5	3– to 5	5
Ankle plantarflexion	5	4	3 to 5	3 to 5	3 to 5-
Ankle dorsiflexion	0	0	0 to 5	2 to 5	1 to 4
Sensory disturbance	Yes	Yes	Yes	No	Yes
Ankle jerk reflex†	A	A	N to A	N to A	D to A
Foot deformity	Yes	Yes	Yes	Yes	Yes
Creatine kinase (IU/L)‡	290	213	63–548	ND	ND
Echocardiography	Constrictive pericarditis	Atrial flutter	Normal	ND	Normal
Lower limb MRI	Anterior calf muscle involvement	Whole calf muscle involvement	Sequential pattern of calf involvement	ND	Calf muscle fatty involvement
Electromyography	Neuropathy, myopathy	Neuropathy, myopathy	Neuropathy, myopathy	Neuropathy	Neuropathy, polyphasic motor units
Muscle biopsy	ND	ND	Size variation, grouping, inclusions§	ND	ND
Reference	This study	This study	4	5	6

*MRC scale: 0=no contraction; 1=trace of contraction; 2=active movement without gravity; 3=active movement against gravity; 4=active movement against gravity and resistance; 5=normal power; †Ankle jerk reflex: N=normal; D=diminished; A=absent; ‡Creatine kinase reference range: 0–170 IU/L; §Marked variation of muscle fiber size and grouping of muscle fiber types. Notably, the electron micrographs frequently revealed subsarcolemmal accumulation of enlarged mitochondria with variable-size rectangular or elongated rhomboidal paracrystalline inclusions in two affected individuals.
CMT2, Charcot-Marie-Tooth disease type 2; dHMN, distal hereditary motor neuropathy; HL, hearing loss; Ho, hoarseness; MRC scale, medical research council scale; ND, not done; PNMHH, peripheral neuropathy, myopathy, hearing loss, and hoarseness.

Supplement). Muscle weakness was observed in all patients. The age range of muscle weakness onset was less broad (4–23 years) than that for HL (Supplementary Fig. 4B in the online-only Data Supplement). However, the severity and involved structures varied between the families. In most cases, HL occurred after muscle weakness except in the affected Canadian patients.

Muscle biopsies in two patients and electromyography yielded clear myopathic evidence in the Korean families. The patient exhibited a creatine kinase level of 548 IU/L, which is 3.2-fold higher than normal. However, myopathy was not diagnosed in the American and Canadian families who were examined using only electromyography (i.e., without muscle biopsies).

MYH14-mutant mice exhibit cardiac myopathy as well as HL,[7] but none of the present affected individuals showed cardiomyopathy. Atrial flutter and constrictive pericarditis were observed in each patient of the second Korean family, but these conditions did not seem to be related to the *MYH14* mutation.

Most mutations in *MYH14* cause nonsyndromic HL, while only the p.R941L mutation exhibits various phenotypes corresponding to syndromic HL. Almutawa et al.[6] suggested that the *MYH14* p.R941L mutation functions in a dominant-negative fashion, inhibiting mitochondrial fission especially in the cell periphery. These reasons for the wide phenotypic spectrum of the PNMHH patients are still valid, but it may also be partly due to differences in race- or individual-specific genetic backgrounds, including genetic modifiers. It is recommended that mutational screening for *MYH14* be performed when PN and HL with or without sensory disturbances occur together in a patient.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2022.18.2.238.

Ethics Statement

The study was approved by the Institutional Review Boards of Sungkyunkwan University, Samsung Medical Center (2014-08-057-002) and Kongju National University (KNU-IRB-2018-62). Written informed consent was obtained from all the participants.

Availability of Data and Material

All data generated or analyzed during the study are included in this published article (and its supplementary information files).

ORCID iDs

Hye Mi Kwon https://orcid.org/0000-0003-3978-1855
Jin Hee Park https://orcid.org/0000-0002-3408-5802
Ki Wha Chung https://orcid.org/0000-0003-0363-8432
Byung-Ok Choi https://orcid.org/0000-0001-5459-1772

Author Contributions

Conceptualization: Hye Mi Kwon, Byung-Ok Choi. Data curation: all authors. Formal analysis: Hye Mi Kwon, Byung-Ok Choi. Funding acquisition: Byung-Ok Choi, Ki Wha Chung. Investigation: Jin Hee Park, Ki Wha Chung. Supervision: Byung-Ok Choi, Ki Wha Chung. Visualization: Hye Mi Kwon, Byung-Ok Choi. Writing—original draft: Hye Mi Kwon, Byung-Ok Choi. Writing—review & editing: Byung-Ok Choi, Ki Wha Chung.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Funding Statement

This work was supported by grants from the National Research Foundation (2019R1A2C1087547, 2020M3H4A1A03084600, and 2021R1A4A2001389) and the Korean Health Technology R&D Project, Ministry of Health and Welfare (HI14C3484 and HI20C0039), Republic of Korea.

REFERENCES

1. Golomb E, Ma X, Jana SS, Preston YA, Kawamoto S, Shoham NG, et al. Identification and characterization of nonmuscle myosin II-C, a new member of the myosin II family. *J Biol Chem* 2004;279:2800-2808.
2. Donaudy F, Snoeckx R, Pfister M, Zenner HP, Blin N, Di Stazio M, et al. Nonmuscle myosin heavy-chain gene MYH14 is expressed in cochlea and mutated in patients affected by autosomal dominant hearing impairment (DFNA4). *Am J Hum Genet* 2004;74:770-776.
3. Kim BJ, Kim AR, Han JH, Lee C, Oh DY, Choi BY. Discovery of MYH14 as an important and unique deafness gene causing prelingually severe autosomal dominant nonsyndromic hearing loss. *J Gene Med* 2017;19:e2950.
4. Choi BO, Kang SH, Hyun YS, Kanwal S, Park SW, Koo H, et al. A complex phenotype of peripheral neuropathy, myopathy, hoarseness, and hearing loss is linked to an autosomal dominant mutation in MYH14. *Hum Mutat* 2011;32:669-677.
5. Iyadurai S, Arnold WD, Kissel JT, Ruhno C, Mcgovern VL, Snyder PJ, et al. Variable phenotypic expression and onset in MYH14 distal hereditary motor neuropathy phenotype in a large, multigenerational North American family. *Muscle Nerve* 2017;56:341-345.
6. Almutawa W, Smith C, Sabouny R, Smit RB, Zhao T, Wong R, et al. The R941L mutation in MYH14 disrupts mitochondrial fission and associates with peripheral neuropathy. *EBioMedicine* 2019;45:379-392.
7. Wang JJ, Rau C, Avetisyan R, Ren S, Romay MC, Stolin G, et al. Genetic dissection of cardiac remodeling in an isoproterenol-induced heart failure mouse model. *PLoS Genet* 2016;12:e1006038.