



# The First Korean Family With Boucher-Neuhäuser Syndrome Carrying a Novel Mutation in *PNPLA6*

Eun Joo Chung<sup>a,b\*</sup>  
 Eunkyong You<sup>c\*</sup>  
 Seung Hwan Oh<sup>d</sup>  
 Go Hun Seo<sup>e</sup>  
 Woo Yeong Chung<sup>f,g</sup>  
 Yun Joong Kim<sup>h</sup>  
 Sang Jin Kim<sup>a,b</sup>

<sup>a</sup>Department of Neurology,  
 Busan Paik Hospital, Inje University  
 College of Medicine, Busan, Korea  
<sup>b</sup>Dementia and Neurodegenerative  
 Disease Research Center,  
 Inje University, Gimhae, Korea

<sup>c</sup>Department of Laboratory Medicine,  
 Busan Paik Hospital, Inje University  
 College of Medicine, Busan, Korea

<sup>d</sup>Department of Laboratory Medicine,  
 Pusan National University  
 Yangsan Hospital, Yangsan, Korea

<sup>e</sup>3billion Inc., Seoul, Korea

<sup>f</sup>Department of Pediatrics,  
 Busan Paik Hospital, Inje University  
 College of Medicine, Busan, Korea

<sup>g</sup>Rare Disease Busan Regional Center,  
 Busan, Korea

<sup>h</sup>Department of Neurology,  
 Yongin Severance Hospital,  
 Yonsei University College of Medicine,  
 Seoul, Korea

**Received** June 24, 2021  
**Revised** October 19, 2021  
**Accepted** October 19, 2021

## Correspondence

Sang Jin Kim, MD, PhD  
 Department of Neurology,  
 Busan Paik Hospital, Inje University  
 College of Medicine,  
 75 Bokji-ro, Buanjin-gu,  
 Busan 47392, Korea  
**Tel** +82-51-890-6425  
**Fax** +82-51-895-6367  
**E-mail** jsk120@hanmail.net

\*These authors contributed equally to this work.

Dear Editor,

Boucher-Neuhäuser syndrome (BNS) (MIM215470) has three key clinical features: cerebellar ataxia, hypogonadotropic hypogonadism, and chorioretinal dystrophy.<sup>1,2</sup> BNS is inherited in an autosomal-recessive pattern and caused by mutations in *PNPLA6* (MIM603197; 19p13.2).<sup>2,3</sup> BNS is one of the disorders associated with *PNPLA6* mutations that form part of a broad neurodegenerative spectrum with a similar phenotypic continuum.<sup>1,3,4</sup>

Here we report two siblings with typical phenotypes and *PNPLA6* mutations of BNS.

A 30-year-old male (proband) and a 29-year-old female (sister of the proband) presented with chorioretinal dystrophy, cerebellar ataxia, and hypogonadotropic hypogonadism. The proband showed a delayed puberty and visual disturbance at the age of 12 years. He had no axillary or pubic hair, and a small penis and testis. Because of the hypogonadotropic hypogonadism, he had taken hormone therapy until the age of 26 years. He also showed mild dysarthria, dysphagia, gaze-evoked nystagmus, and peripheral neuropathy.

The sister of the proband presented with cerebellar ataxia and visual disturbances in her teens. She could not almost walk without assistance at the age of 28 years. She also showed dysarthria and alopecia. However, both siblings had never shown neurocognitive impairments. Serum testosterone of the proband was low. Follicle-stimulating hormone and luteinizing hormone were low in both siblings.

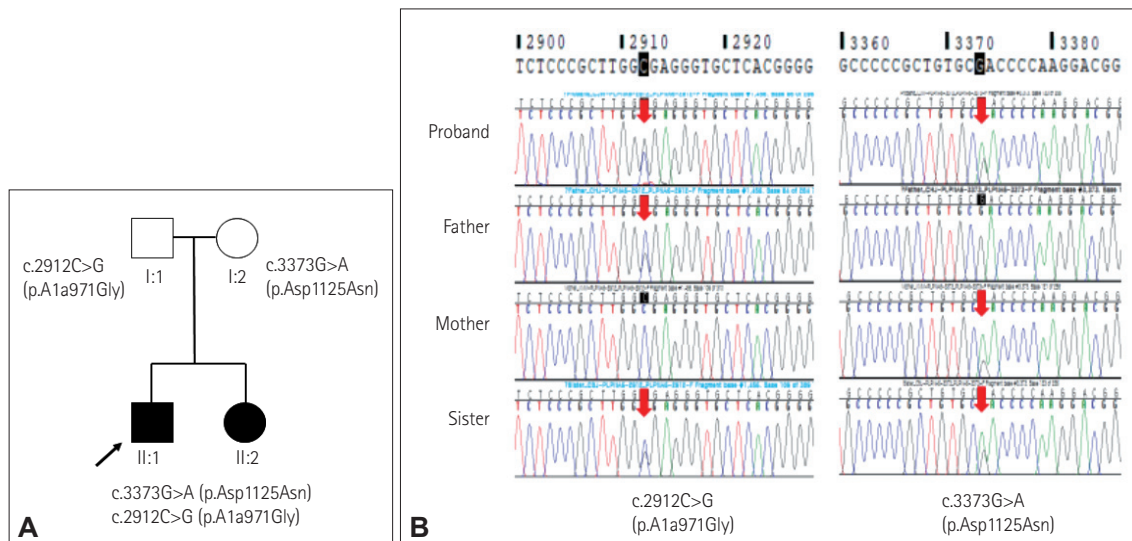
Electromyography of the proband produced normal findings, but a nerve conduction study showed no responses in the left common motor and superficial sensory peroneal nerves (Supplementary Fig. 1A in the online-only Data Supplement). Brain MRI of both siblings revealed prominent cerebellar atrophy, which was more severe in the proband (Supplementary Fig. 1B and C in the online-only Data Supplement).

In addition to the triad of clinical key features in BNS, ocular motor abnormalities, dysarthria, pyramidal tract signs, peripheral neuropathy, short stature, hair anomalies, and cognitive dysfunction have also commonly been reported.<sup>2-4</sup> Both of the present siblings showed various clinical features in addition to the classical triad of features.

Clinical, laboratory, and electrophysiological findings are listed in Supplementary Table 1 (in the online-only Data Supplement). The two compound heterozygous mutations identified by whole-exome sequencing in both siblings comprised c.3373G>A (p.D1125N), which is a previously reported mutation, while c.2912C>G (p.A971G) is a novel mutation that has not been reported previously (Fig. 1). Compound heterozygous variants of both siblings were transmitted from the mutation carried by each parent. They are categorized as “likely pathogenic” variants by the American College of Medical Genetics guidelines.<sup>5</sup>

Both compound heterozygous mutations of the two siblings were located in the phospholipid esterase domain (EST) of *PNPLA6*, which encodes neuropathy target esterase (NTE) that participates in phosphatidylcholine metabolism.<sup>4</sup> Most *PNPLA6* mutations are located in the EST, which affects the esterase activity of NTE, and *PNPLA6* expression has been noted

© This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.



**Fig. 1.** Family pedigree and electropherograms of the *PNPLA6* gene. A: The parents of the siblings each had one of the two *PNPLA6* mutations. B: Compound heterozygous variants of the proband (II:1) and his sister (II:2) were inherited from both of their parents and caused their symptoms. The mother (I:2) had a missense heterozygous mutation, c.3373G>A (p.D1125N), in exon 29, and the father (I:1) had a missense heterozygous mutation, c.2912C>G (p.A971G), in exon 25.

in the central nervous system and retina.<sup>4</sup> Different impairments of NTE activity in *PNPLA6*, rather than the location of pathogenic variants, result in different clinical combinations.<sup>3,4,6</sup> A greater reduction of NTE activity leads to more-severe and early-onset phenotypes.<sup>3,4</sup> The clinical features and course of the same mutation different both between and within families.<sup>3,4,6</sup> Therefore, it is necessary to continuously evaluate the phenotype–genotype correlation in BNS.

### Supplementary Materials

The online-only Data Supplement is available with this article at <https://doi.org/10.3988/jcn.2022.18.2.233>.

### Ethics Statement

This work was approved by the institutional review board of Inje University Busan Paik Hospital (IRB No. BPIRB 2021-04-037-002). Written informed consent was obtained from both siblings and their parents before performing gene analyses.

### 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

Eun Joo Chung	<a href="https://orcid.org/0000-0001-8948-1135">https://orcid.org/0000-0001-8948-1135</a>
Eunyoung You	<a href="https://orcid.org/0000-0002-6836-499X">https://orcid.org/0000-0002-6836-499X</a>
Seung Hwan Oh	<a href="https://orcid.org/0000-0002-1946-9939">https://orcid.org/0000-0002-1946-9939</a>
Go Hun Seo	<a href="https://orcid.org/0000-0003-1518-1791">https://orcid.org/0000-0003-1518-1791</a>
Woo Yeong Chung	<a href="https://orcid.org/0000-0002-5024-7285">https://orcid.org/0000-0002-5024-7285</a>
Yun Joong Kim	<a href="https://orcid.org/0000-0002-2956-1552">https://orcid.org/0000-0002-2956-1552</a>
Sang Jin Kim	<a href="https://orcid.org/0000-0001-7240-2154">https://orcid.org/0000-0001-7240-2154</a>

### Author Contributions

Conceptualization: Eun Joo Chung, Sang Jin Kim. Data curation: Seung

Hwan Oh, Yun Joong Kim. Formal analysis: Woo Yeong Chung. Methodology: Eunyoung You. Software: Go Hun Seo. Writing—original draft: Eun Joo Chung. Writing—review & editing: Eunyoung You, Seung Hwan Oh, Go Hun Seo, Woo Yeong Chung, Yun Joong Kim, Sang Jin Kim.

### Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

### Funding Statement

None

### REFERENCES

- Zheng R, Zhao Y, Wu J, Wang Y, Liu JL, Zhou ZL, et al. A novel *PNPLA6* compound heterozygous mutation identified in a Chinese patient with Boucher-Neuhäuser syndrome. *Mol Med Rep* 2018;18:261-267.
- Tarnutzer AA, Gerth-Kahlert C, Timmann D, Chang DI, Harmuth F, Bauer P, et al. Boucher-Neuhäuser syndrome: cerebellar degeneration, chorioretinal dystrophy and hypogonadotropic hypogonadism: two novel cases and a review of 40 cases from the literature. *J Neurol* 2015;262:194-202.
- Synofzik M, Gonzalez MA, Lourenco CM, Coutelier M, Haack TB, Rebelo A, et al. *PNPLA6* mutations cause Boucher-Neuhauser and Gordon Holmes syndromes as part of a broad neurodegenerative spectrum. *Brain* 2014;137:69-77.
- Hufnagel RB, Arno G, Hein ND, Hershenson J, Prasad M, Anderson Y, et al. Neuropathy target esterase impairments cause Oliver-McFarlane and Laurence-Moon syndromes. *J Med Genet* 2015;52:85-94.
- Seo GH, Kim T, Choi IH, Park JY, Lee J, Kim S, et al. Diagnostic yield and clinical utility of whole exome sequencing using an automated variant prioritization system, EVIDENCE. *Clin Genet* 2020;98:562-570.
- Knoch S, Majewski J, Ramamurthy V, Cao S, Fahiminiya S, Ren H, et al. Mutations in *PNPLA6* are linked to photoreceptor degeneration and various forms of childhood blindness. *Nat Commun* 2015;6:5614.