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Short Report

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Novel Pathogenic Variant (c.1171A>T) in *PHF21A* in a Female with Intellectual Disability and Craniofacial Anomalies

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Neurodevelopmental disorders · *PHF21A* · Potocki-Shaffer syndrome · Whole exome sequencing

Abstract
Background: *PHF21A*, along with *EXT2* and *ALX4*, is one of the causative genes of Potocki-Shaffer syndrome (PSS), a rare contiguous disorder involving chromosome region11p11.2. *PHF21A* has been associated with intellectual developmental disorders and craniofacial anomalies and suggested as a candidate for more extended phenotypes. However, variants in *PHF21A* and its associated phenotypes are yet to be fully explored, since reports on cases with variants affecting this gene are few worldwide. We present a novel heterogeneous variant in *PHF21A* in a 26-year-old Korean female. ***Methods:*** The patient's clinical manifestations were recorded and physical examination, cognitive assessment, brain imaging, metabolic screening, and cytogenetic testing including whole exome sequencing were pursued. ***Results:*** Whole exome sequencing identified a de novo nonsense variant c.1171A>T (p.Lys391Ter), affecting the AT-hook domain. The patient showed an extended phenotypic spectrum along with intellectual developmental disorders and craniofacial anomalies, such as attention-deficit hyperactivity disorder, epilepsy, overgrowth, and hypotonia. Variants affecting the AT-hook domain are few in PSS, however, the phenotypic spectrum of the patient was in line with previously reported cases. ***Conclusion:*** This case further reinforced and adds to the extended data on the phenotypes associated with *PHF21A* haploinsufficiency.

Introduction

PHF21A, along with *EXT2* and *ALX4*, is 1 of the 3 causative genes of Potocki-Shaffer syndrome (PSS), a rare contiguous disorder involving chromosome region 11p11.2. A few cases with disruption of *PHF21A* due to balanced translocations and gross deletions in the region have been reported [Kim et al., 2012; Labonne et al., 2015; McCool et al., 2017]. Reports on cases with sequence variants affecting this gene are even fewer; to date, only 11 pathogenic variants in *PHF21A* (8 frameshifts, 2 nonsense, and 1 missense) in 12 different individuals have been reported worldwide [Hamanaka et al., 2019; Kim et al., 2019; Satterstrom et al., 2020].

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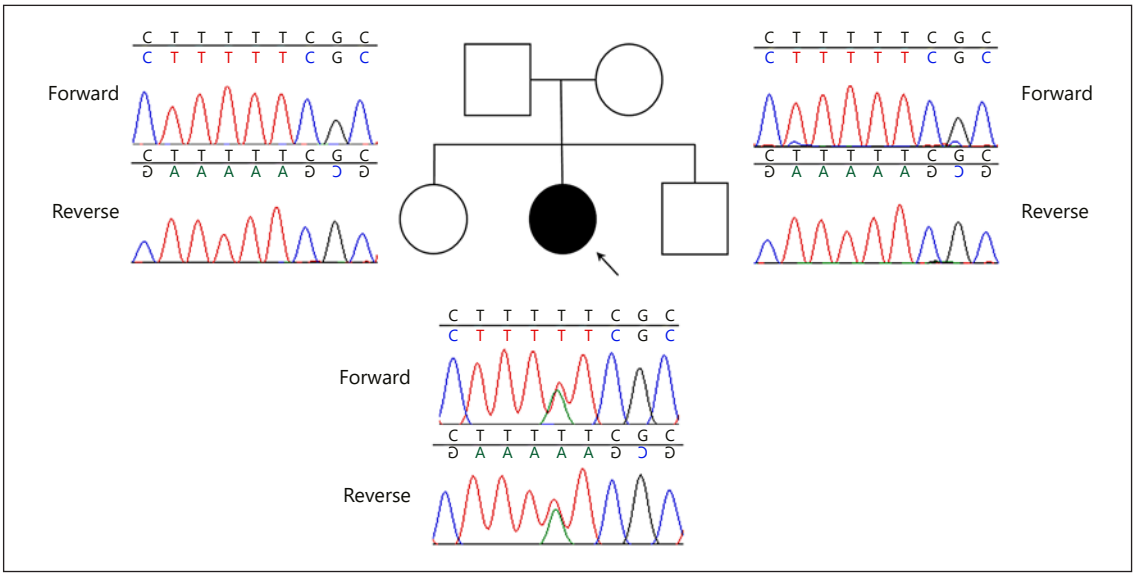

Fig. 1. Sanger sequencing results in trios. The proband (marked with an arrow) had a de novo novel nonsense variant in the *PHF21A* gene (NM_00110802.1: c.1171A>T).

Due to its haploinsufficiency mechanism, *PHF21A* has been associated with intellectual developmental disorders and craniofacial anomalies [Kim et al., 2012; Labonne et al., 2015; McCool et al., 2017]. More recently, an extended phenotypic spectrum has been implicated, including autism spectrum disorder, attention-deficit hyperactivity disorder (ADHD), epilepsy, overgrowth, hypotonia, and finger anomalies [Hamanaka et al., 2019; Kim et al., 2019].

Here, we report a novel heterogeneous de novo nonsense variant in *PHF21A* identified in a 26-year-old Korean female. We herein described her phenotype compared to previous publications with the aim to examine the phenotypic spectrum associated with *PHF21A*.

Case Report

The patient was born at term after an uneventful pregnancy with a birth weight of 3.5 kg (>50th percentile) from non-consanguineous healthy parents. Her family history was negative for neurodevelopmental disorders. She manifested signs of developmental delay and intellectual disability and was diagnosed with intellectual disability at 5 years of age. Other neurobehavioral concerns included ADHD, self-harming behaviors, and poor eye contact. At 12 years of age, she presented with generalized tonic-clonic seizure, for which she was evaluated for the first time at the Korea University Guro Hospital. Electroencephalogram recorded high-voltage sharp waves in the left temporo-occipital region. Physical examination revealed mild hypotonia and mild craniofacial dysmorphism, including mild to moderate plagiocephaly, prominent supraorbital ridge, relatively small ears with the right ear positioned posteriorly than the left, and gaping mouth. Other physical findings include relatively short fingers without signs of clinodactyly or syndactyly, flat feet, and atopic skin lesions on both her hands and forearms, in particular. Signs of postnatal overgrowth manifested as a weight of 61 kg (97th percentile) with a height of 162.5 cm (97th percentile) at 12 years. Severe intellectual disability (Korean Wechsler Intelligence Scale for Children-III, scores <0.1%) and significant ADHD (Conners scale for ADHD assessment, T-score 77) were diagnosed. Other tests completed for this patient over time included metabolic screening, chromosomal karyotyping, Prader-Willi and Angelman study, and brain MRI, all of which were normal.

Genetic Evaluation

Whole exome sequencing (WES) was performed for the patient at 23 years of age, as previously described [Seo et al., 2020]. Briefly, all exon regions were captured using the SureSelect kit (Version C2; Agilent Technologies, Inc., Santa Clara, CA, USA) and were sequenced using the Novaseq 6000 (Illumina, San Diego, CA, USA). Common variants reported in population genome databases, including gnomAD (http://gnomad.broadinstitute.org/) and 3billion Inc (https://3billion.io/), were filtered by a minor allele frequency of >5%. The variants were then prioritized based on the evidence of pathogenicity obtained from disease databases, including OMIM (www.omimorg), ClinVar, and UniProt, and the patient's clinical phenotype according to the 2015 American College of Medical Genetics and Genomics (ACMG) guidelines [Richards et al., 2015]. A heterogeneous nonsense variant, *PHF21A* (NM_00110802.1): c.1171A>T (p.Lys391Ter), was identified and confirmed by Sanger sequencing (Fig. 1). Based on the 2015 ACMG guidelines, the c.1171A>T variant is considered pathogenic because (1) this substitution creates a premature stop codon (p.Lys391Ter) in exon 12, producing a truncated protein of 390 amino acids compared to the wild type *PHF21A* of 680 amino acids

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Table 1. Summary of the clinical features of patients with mutations of *PHF21A*

	Our patient	Hamanaka et al. [2019]			Kim et al. [2019]						
Age, years	26	3	5	9	13	3	9	10	18	6	18
Sex	Female	Male	Male	Male	Female	Male	Female	Male	Male	Male	Female
Exon	12	12	17	8	18	13	18	17	15	17	18
Nucleotide change NM_001101802.1	c.1171A>T	c.1220dupC	c.1738C>T	c.657_658insAA	c.1955delC	c.1285G>A	c.1956delT	c.1738C>T	c.1471dupT	c.1738C>T	c.2024delA
Effect on protein NP_001095272.1	p.Lys391Ter	p.Glu408ArgfsTer3	p.Arg580Ter	p.Pro220AsnfsTer48	p.Pro652LeufsTer104	p.Gly429Ser	p.Pro652ProfsTer104	p.Arg580Ter	p.Cys491LeufsTer81	p.Arg580Ter	p.Gln675ArgfsTer81
Inheritance	De novo	De novo	De novo	De novo	De novo	De novo	De novo	De novo	Not found in mother	De novo	De novo
Cranial anomalies	Plagiocephaly	Plagiocephaly	Metopic ridge	Macrocephaly	Macrocephaly	–	–	Plagiocephaly	–	–	Macrocephaly
Facial anomalies	+	+	N/A	+	+	+	+	+	–	+	+
Forehead	Prominent supraorbital ridge	Frontal bossing			Pronounced widow's peak	High forehead					
Eyebrows						Synophrys					Sparse lateral eyebrows
Eyes				Downslanting palpebral fissures, mild hypertelorism	Significant bilateral epicanthal folds			Hypertelorism			Telecanthus
Nose		Depressed nasal bridge, small nose with anteverted nares		Slightly broad nasal bridge, smooth but not short philtrum	Broad nasal bridge,a broad nasal tip, wide, short, and hypoplastic columella	Broad nasal bridge					
Mouth	Opened mouth	Downturned mouth with tent-shaped upper lip		Downturned corners of the mouth	Opened mouth	Macrostomia with conical teeth	Thinner upper lip			Thinner upper lip	Prominent cupid bow configuration of the upper lip
Ears	Small ears				Low-set and posteriorly rotated fleshy ears, Darwinian tubercle on the left ear and an ear length of 6 cm				Large earlobes		Left preauricular pit
General contours and others					Abundant scalp hair, one café-au lait spot, several moles on the head below the hairline	Round face, mild bitemporal narrowing	Prominent chin			Prominent chin, midface hypoplasia	Slack facial expression
Other physical anomalies	Flat feet, atopic skin lesions on both hands and forearms	N/A	N/A	N/A	Completely flat feet, brachydactyly of the toes, inverted left nipple and supernumerary nipple on the left	Syndactyly of the second and third toes on both feet		Hip dysplasia, valgus feet			
Intellectual disability	+	+	+	+	+	+	+	+	+	+	+
Developmental delay	+	+	+	+	+	+	+	+	+	+	+
Language delay	+	+	+	+	+	+	+	+	+	+	+
ADHD	+	N/A	+	+	+	N/A	+	+	+	–	N/A
Autism	–	N/A	+	–	+	N/A	–	–	+	–	+
Seizures	+	+	N/A	–	+	+	+	+	–	–	–

Table 1 (continued)

	Our patient	Hamanaka et al. [2019]			Kim et al. [2019]								
Finger anomalies													
Tapering fingers	–	+	–	–	+	+	+	–	–	–	–	–	–
Clinodactyly	–	N/A	N/A	N/A	+	+	+	–	+	–	–	–	–
Syndactyly	–	N/A	N/A	N/A	–	+	–	+	–	–	–	–	–
Hypotonia	+/–	+	N/A	+	+	+	+	N/A	–	–	–	–	–
Obesity	+	N/A	N/A	+	+	–	+	–	+	–	–	–	+
Overgrowth	+	+	N/A	+	+	+	N/A	N/A	+	+	+	+	+

N/A: not available. The 2 patients with frameshift variants NM_001101802.3(*PHF21A*): c.840delC (p.Ile281SerfsTer14) (exon 9) and c.1153delA (p.Ser385AlafsTer30) (exon 12), respectively, of Satterstrom et al. [2020] were not listed in the table since clinical features listed in the table were not available for them, except for the presence of autism spectrum disorders.

(NP_001095272.1). This nonsense variant causes loss of normal protein function through nonsense-mediated mRNA decay (PVS1); (2) this variant is absent from population databases, such as the Genome Aggregation Database (https://gnomad.broadinstitute.org/) and Exome variant server (https://evs.gs.washington.edu/EVS/) (PM2), and (3) the variant is observed to have arisen de novo (PM6) (Fig. 1). Array-CGH levels were normal.

Result and Discussion

PHF21A is known to encode BHC80, a subunit of the KDM1A multiprotein complex that regulates neuronal genes during embryogenesis via maintenance of histone demethylation [Garay et al., 2016]. Orthologous suppression of *PHF21A* in a zebrafish model resulted in abnormalities in the development of the head, face, and jaw, supporting the role of *PHF21A* in craniofacial abnormalities [Kim et al., 2012]. There were higher transcription levels of *PHF21A* in the brain and skeletal muscle than in any other organs, further supporting its relation to neurological phenotypes [Kim et al., 2019].

The clinical findings of our case showed an extended phenotypic spectrum along with intellectual developmental disorders and craniofacial anomalies, such as ADHD, epilepsy, overgrowth, and hypotonia. The phenotypic spectrum of previously reported cases are shown in Table 1. Our case is in line with previously reported cases, suggesting disruption of *PHF21A* possibly contributes to syndromic intellectual disability and craniofacial anomalies with variable neurological phenotypes. Additional clinical signs confined to our case were atopic skin lesions on both hands and forearms, but their relation to the role of the gene remains inconclusive at present and needs further studies.

PHF21A contains regions of a AT-hook domain (aa 427–437 in NP_001095271.1), plant homeodomain (PHD) finger domain (aa 486–532), 2 leucine zipper domains (aa 33–54 and aa 586–607), and intrinsically disordered region (IDR) domain (aa 639–680) [Kim et al., 2012, 2019]. Previously reported cases were mostly predicted to affect leucine zipper domains and/or IDR domain and only 2 cases with frameshift variants with a AT-hook domain truncation have been reported [Hamanaka et al., 2019; Kim et al., 2019]. Among the cases we reviewed, 4 variants were predicted to elicit NMD, while other 4 were not. However, significant phenotype differences were not explicit between these 2 groups.

The limitation in our study is that we could not contribute to provide the evidence regarding the role of each domain nor functional mechanisms behind it. However,

for our case has a truncated protein of which disruption started from the AT Hook domain, it provides direct evidence supporting *PHF21A* haploinsufficiency as a cause of neurodevelopmental disorders and craniofacial anomalies that have been described in the PSS patients in the literature.

In conclusion, we identified a novel *PHF21A* variant in a Korean female patient. This case further reinforced *PHF21A* haploinsufficiency as a cause of neurological and developmental impairment and craniofacial anomalies in PSS.

Statement of Ethics

This study was approved by the Institutional Review Board of the Korea University Guro Hospital, Seoul, Korea (IRB-2021GR0049). Written informed consent was obtained from the parent/legal guardian of the patient for publication of the details of the medical case and any accompanying images.

Conflict of Interest

The authors declare no conflict of interest.

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Author Contributions

C.L. and J.Y. drafted the manuscript. C.L., J.Y., and B.G.P. analyzed the data. J.A.K and B.L.E. designed and supported the project.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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