Case Report
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Variant of *CHD1* gene resulting in a Korean case of Pilarowski-Bjornsson syndrome

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Many monogenic neurodevelopmental disorders have been newly identified in recent years owing to the rapid development of genetic sequencing technology. These include variants of the epigenetic machinery – up to 300 known epigenetic factors of which about 50 have been linked to specific clinical phenotypes. Chromodomain, helicase, DNA binding 1 (*CHD1*) is an ATP-dependent chromatin remodeler, known to be the causative gene of the autosomal dominant neurodevelopmental disorder Pilarowski-Bjornsson syndrome. Patients exhibit various degrees of global developmental delay, autism, speech apraxia, seizures, growth retardation, and craniofacial dysmorphism. We report the first case of Pilarowski-Bjornsson syndrome in Korea, due to a de novo missense variant of the *CHD1* gene (c.862A>G, p.Thr288Ala) in a previously undiagnosed 17-year-old male. His infantile onset of severe global developmental delay, intellectual disability, speech apraxia, and failure to thrive are compatible with Pilarowski-Bjornsson syndrome. We also noted some features not previously reported in this syndrome such as skeletal dysplasia and ichthyosis. Further studies are needed to discover the specific phenotypes and pathogenic mechanisms behind this rare disorder.

Key words: Pilarowski-Bjornsson syndrome, *CHD1*, Neurodevelopmental disorder, Speech apraxia, Skeletal dysplasia.

Introduction

With the evolution of genetic sequencing technology, several monogenic neurodevelopmental disorders have been identified. Among the most recent are variants of the epigenetic machinery, composed of readers, writers, erasers, and chromatin remodelers. There are currently 300 known epigenetic factors, of which approximately 50 have been linked to specific clinical phenotypes [1,2]. The chromodomain, helicase, DNA binding (CHD) family, comprising CHD1 through CHD9, is an ATP-dependent chromatin remodeler [3]. Pathogenic variants in these genes lead to a wide variety of phenotypes that share common features, such as intellectual disability, autism, and abnormal head size. Examples include Snijders Blok-Campeau syndrome (*CHD3*), Sifrim-Hitz-Weiss syndrome (*CHD4*), and Zahir Friedman syndrome (*CHD8*). CHARGE syndrome, which is associated with *CHD7*, is mainly considered a congenital anomaly – however, these patients may also present neurodevelopmental abnormalities. Those with specific variants of *CHD1* have been recognized as a separate disease entity since 2018, i.e., the autosomal

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dominant neurodevelopmental disorder Pilarowski-Bjornsson syndrome [4]. Patients show varying degrees of hypotonia, global developmental delay, autism, speech apraxia, seizures, growth retardation, and craniofacial dysmorphism. Less than 10 cases of Pilarowski-Bjornsson syndrome have been reported worldwide to date, and most reports lack phenotypic data. Clinvar database search in August 2022 revealed a total of 50 missense variants in *CHD1*, mostly that have been classified as variants of uncertain significance according to the American College of Medical Genetics (ACMG) guidelines [5].

Here, we report the first Korean case of Pilarowski-Bjornsson syndrome caused by a de novo missense variant of *CHD1*, c.862A>G (p.Thr288Ala), in a previously undiagnosed 17-year-old male with infantile onset of severe developmental delay, speech apraxia, failure to thrive, skeletal dysplasia, and skin rash.

Case

The proband was born at GA 36 weeks with a weight of 1.65 kg (<3rd percentile). He received care in neonatal intensive unit for a month because of his small weight but did not require respiratory support. The results of neonatal metabolic screening tests were within normal limits. The family history of the proband was unremarkable, and included healthy, unaffected, and unrelated Korean parents and a younger sister. The patient was diagnosed with craniosynostosis and underwent corrective surgery at 2 years of age. Brain imaging was otherwise unremarkable, with no apparent brain atrophy. Karyotyping performed in an external hospital shortly after birth revealed normal results, and the patient was subsequently lost to pediatric outpatient follow-up as parents did not seek further genetic testing.

The patient visited the pediatric orthopedic surgery clinic for dislocated right knee, genu valgum, and thoracolumbar scoliosis at 11 years of age. X-ray and magnetic resonance imaging of the knee and spine combined with skeletal survey were consistent with multiple epiphyseal dysplasia, multiple fragmented, hypoplastic ossification centers of the long bones and height loss of all epiphyses with epiphyseal irregularity, in contrast to relatively normal-looking vertebral bodies (Fig. 1). He underwent corrective operations for the dislocated right knee and scoliosis at 10 and 15 years of age, respectively.

The patient was referred to our pediatric genetic clinic for a proper genetic diagnosis at 15 years of age. A detailed history revealed a marked global developmental delay from early infancy, as he could only creep and not walk until 4 years of age. Intellectual disability was prominent, his objective cognitive function at 15 years of age was found to be equivalent to that of a preschooler according to the Korean developmental screening test, and his best gross motor performance was gait-assisted. He also showed marked fine motor delays that required assistance in most daily activities. Language disabilities consistent with speech apraxia were noted, such as effortful initiation of speech, abnormal rhythm, stress, and intonation. The features of autism were not definite. The patient had no history of seizures. His height was 133 cm, weight was 19.2 kg, and head circumference was 46 cm, which were all well below the 3rd percentile for his age. Facial dysmorphism was noticeable on physical examination, including wide-set eyes, downslanted palpebral fissures, a low nasal bridge, and bilateral microtia. The patient also had a whole-body rash consistent with ichthyosis. Laboratory tests were unremarkable for complete blood cell count, electrolytes, creatinine, and liver enzymes. Echocardiography results were

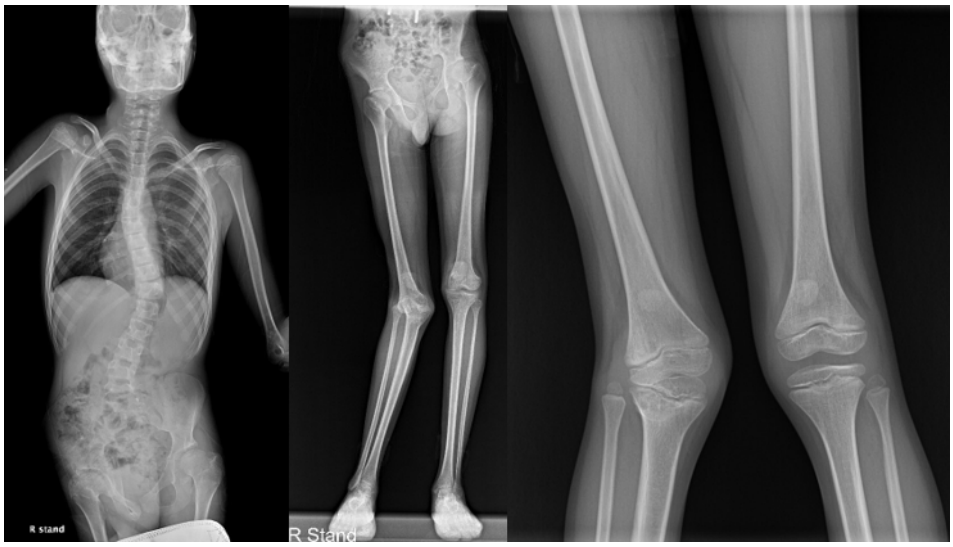

Fig. 1. Skeletal X-rays of the patient, showing severe scoliosis, fragmented, hypoplastic ossification centers in the long bones, and epiphyseal irregularity in contrast to relatively normal looking vertebral bodies.

within normal limits.

Targeted panel gene sequencing for multiple epiphyseal dysplasia including 10 known causative genes (*COMP, CANT1, COL2A1, COL9A1, COL9A2, COL9A3, MATN3, SLC26A2, DDR2,* and *UFSP2*), was performed, and the result was negative. The patient participated in the National Project of Bio Big Data, and whole-genome sequencing was performed on the proband and his parents. A de novo heterozygous missense variant of *CHD1*, c.862A>G (p.Thr288Ala), likely pathogenic according to the ACMG classification, was identified and confirmed by Sanger sequencing.

Discussion

Evidently, this is the first reported case of Pilarowski-Bjornsson syndrome in Korea, with a detailed clinical case description. Early development of the brain requires extreme plasticity. This is thought to be achieved by dynamic regulation of gene expression in response to external stimuli, through epigenetic modifications of chromatin such as acetylation, phosphorylation, methylation, ubiquitination and sumoylation [6]. As mentioned above, the CHD family is recognized as a key epigenomic programmer in cellular and model organism studies, and the natural dysregulation of this role is hypothesized to result in disease occurence [7,8].

CHD1 was mapped to the long arm of chromosome 5. It encodes a highly conserved protein with two chromodomains that bind to histone components and control chromatin opening, transcript elongation, and histone positioning [9]. *CHD1* is ubiquitously expressed in the bone marrow, lymph nodes, intestines, ovary/testis, and brain, especially in the cerebellum and basal ganglia [10]. A study using the aquatic model *Xenopus*, demonstrated that *CHD1* is required for cranial neural crest development, and jaw cartilage formation, and is therefore critical for craniofacial development [11].

In 2018 through whole exome sequencing, Pilarowski et al. [4] identified six females with heterozygous missense variants of *CHD1* among large groups of patients with neurodevelopmental abnormalities. Patients exhibited common phenotypes, such as hypotonia, severe developmental delay, and variable phenotypes, including autism with stereotypies, speech apraxia, seizures, growth retardation, craniofacial dysmorphism, and mild immune abnormalities. Functional studies have revealed a global increase in closed chromatin modification in patient-derived cells compared to that in control cells, suggesting pathogenicity. Three similar missense mutations in *CHD1* were identified in a large cohort of patients with autism, but other clinical information was unavailable [12-14]. One patient with a large deletion encompassing *CHD1* was reported to be neurodevelopmentally normal, supporting a dominant -negative mechanism of action [15].

The missense variant c.862A>G (p.Thr288Ala) identified in *CHD1* is located at the third base of exon 8 among a total of 37 exons. The nucleotide variant is hypothesized to alter its own splicing as it sits on the exonic splicing enhancer. It has not been reported in the literature and is absent from control databases, such as EXaC 100 and gnomAD (v3). The variant affects an evolutionarily highly conserved residue in humans, rhesus monkeys, mice, dogs, elephants, chickens, western clawed frogs, and zebrafish species (phyloP100way=5.96). The variant affects an evolutionarily conserved residue (phyloP100way=5.96). Eleven out of the nineteen in silico prediction tools in Varsome predicted this variant to be deleterious (Sorting Intolerant From Tolerant score=–0.007, Protein Variation Effect Analyzer score=4.41) [16]. This mutation was absent in parents whose paternity and maternity were confirmed. Therefore, according to ACMG guidelines, this novel variant qualifies as likely pathogenic.

Our patient showed some degree of phenotypic compatibility with previously reported Pilarowski-Bjornsson syndrome cases such as early onset developmental delay and growth failure, severe intellectual disability, speech apraxia, and similar dysmorphic features such as wide-set eyes, downslanted palpebral fissures, and a low nasal bridge. However, the patient first presented skeletal dysplasia and a whole-body rash, both of which have not been reported in other patients. Although the exact mechanism is unknown, diseases related to epigenetic machinery are known to have largely variable phenotypes. This may explain the unique findings of our patient. This could also be due to the patient's sex and racial background being different compared to previous reports.

The most remarkable feature of this patient was that he exhibited skeletal abnormalities, namely, epiphyseal dysplasia of the long bone in the whole body and not limited to the craniofacial area. The expression of genes regulated by *CHD1* is induced during osteoblast differentiation [17]. Depletion of *CHD1* stalls RNA polymerase II, and histone occupancy is limited to the transcription start site of the target osteogenic loci. Although no functional studies have been performed, we hypothesized that disruption of osteoblast differentiation by abnormal *CHD1* may have played a role in causing skeletal dysplasia in our patient. These abnormalities may also partly explain his microcephaly instead of macrocephaly, as in case of other patients.

Ichthyosis, a disorder of the epidermis characterized by scaling, hyperkeratosis or erythroderma, also appears to be unique

to our patient. Ichthyosis is implicated in many genetic syndromes with neurological manifestations, because the brain and skin originate from the same neuroectodermal layer [18]. As ichthyosis is a rather uncommon yet distinct skin manifestation, these findings in our patient may indicate a novel manifestation of this disease.

In conclusion, we describe a Korean male with Pilarowski-Bjornsson syndrome caused by a novel missense mutation in *CHD1*. He showed growth failure, global developmental delay, intellectual disability, speech apraxia, and facial dysmorphism, compatible with the aforementioned syndrome. Based on this patient, we propose multiple skeletal dysplasia and skin diseases as possible related phenotypes. Further investigation is warranted to discover specific pathogenic mechanisms, and identification of more patients with detailed phenotypic information is needed to paint a clearer clinical picture of this rare disease.

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Authors' Contributions

Conception and design: YS. Acquisition of data: SHS, HJK, MSP. Analysis and interpretation of data: YS, AC. Drafting the article: YS. Critical revision of the article: AC. Final approval of the version to be published: AC.

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