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Novel *HSD17B4* Variants Cause Progressive Leukodystrophy in Childhood: Case Report and Literature Review

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Abstract

D-bifunctional protein (DBP) deficiency is a peroxisomal disorder with a high degree of phenotypic heterogeneity. Some patients with DBP deficiency develop progressive leukodystrophy in childhood. We report a 6-year-old boy with moderate hearing loss who presented with developmental regression. Brain magnetic resonance imaging demonstrated progressive leukodystrophy. However, very long chain fatty acids (VLCFAs) in the plasma were at normal levels. Whole-exome sequencing revealed compound heterozygous variants in *HSD17B4* (NM_000414.3:c.[350A > T];[394C > T], p.[[Asp117Val]];[[Arg132Trp]]). The c.394C > T variant has been identified in patients with DBP deficiency and is classified as likely pathogenic, while the c.350A > T variant was novel and classified as uncertain significance. Although one of the two variants was classified as uncertain significance, an accumulation of phytanic and pristanic acids was identified in the patient, confirming type III DBP deficiency. DBP deficiency should be considered as a diagnosis in children with progressive leukodystrophy and hearing loss even if VLCFAs are within normal levels.

Keywords

D-bifunctional protein deficiency, *HSD17B4*, peroxisomal disease, leukodystrophy, very long chain fatty acids, sensorineural hearing loss

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Introduction

The hydroxysteroid 17-beta dehydrogenase 4 (*HSD17B4*) gene encodes the D-bifunctional protein (DBP), which is a multifunctional enzyme that catalyzes the second and third steps of peroxisomal β-oxidation of fatty acids and their derivatives. DBP has three functional domains: 3-hydroxyacyl-CoA dehydrogenase, 2-enoyl-CoA hydratase, and sterol carrier protein 2-like domain.[1] Biallelic variants in *HSD17B4* have been reported to cause DBP deficiency (OMIM#261515) and Perrault syndrome (OMIM#233400) in an autosomal recessive manner. Depending on which of the three functional domains is deficient, DBP deficiency can be classified into three types. Type I has deficiency of both the hydratase and dehydrogenase units, while types II and III have isolated hydratase and dehydrogenase deficiencies, respectively.

The clinical phenotype of type I DBP patients is very severe and patients die within the first 14 months of life. Except for a few cases, both type II and type III patients also have a severe disease course.[2] Common symptoms of typical early-onset DBP include neonatal hypotonia, seizures within the first month of life, intellectual disability, progressive loss of vision and hearing, and specific facial features. The majority of patients die before the age of 2 years. Brain magnetic resonance imaging

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(MRI) has demonstrated polymicrogyria, generalized hypoplasia, and demyelination, while biochemical findings show an increase in very long chain fatty acids (VLCFAs) in the plasma.[3]

Recently, the clinical spectrum caused by biallelic *HSD17B4* variants has expanded with advances in sequencing technology. Increasing numbers of case reports of DBP deficiency with juvenile onset or surviving until adulthood have been reported, with patients presenting with progressive sensorineural hearing loss, ataxia, peripheral neuropathy, and other neurological signs. Brain MRIs of these patients show progressive cerebellar atrophy, but serum VLCFA levels are within normal ranges in many cases.[4] Additionally, biallelic *HSD17B4* variants have been reported to cause Perrault syndrome, in which ovarian dysgenesis in females and sensorineural hearing loss in both males and females are observed. Pierce et al. indicated a clinical overlap between Perrault syndrome and DBP deficiency in adolescents.[5]

Here, we report a 6-year-old boy with DBP deficiency caused by novel compound heterozygous *HSD17B4* variants whose brain MRI showed progressive white matter dystrophy in childhood. We also review similar cases in the literature.

Case

The patient is a 6-year-old Japanese boy who was born full-term without neonatal asphyxia.

He showed developmental delay from infancy. In terms of gross motor skills, he was able to hold his head up at the age of 5 months, sit without support at 7 months, and walk with support at 20 months. For fine motor skills, he was able to grip at 10 months of age. In terms of language, he spoke a few meaningful words at 20 months of age. His developmental level reached its peak at 36 months of age. His symptoms have progressed as follows.

Repeated examinations of the auditory brainstem response (ABR) at birth and 1 month of age revealed congenital bilateral moderate hearing loss (50 dB). His reaction to the sound continued to be poor. At the age of 4 years, the ABR was absent, including wave I.

Spasticity with lower extremity predominance was observed after 2 years of age. From the age of 4 years, the spasticity spread to the entire body, and he was unable to walk. He then showed truncal ataxia and dystonia. From the age of 4 and half years, he developed epilepsy and was unable to sit alone. He became bedridden at 5 years old. Recently he has developed speaking and swallowing difficulties and low activity levels.

MRI initially showed T2-weighted hyperintensity in the deep white matter of the occipital lobe, cerebral peduncle, and pyramidal tract of the brainstem (Figure 1A–C, H–J). The thalamus and basal ganglia remained normal in the early stages of the disease, until 2 years of age. T2-weighted hyperintensity in the white matter gradually spread to the corpus callosum ampulla, thalamus, and basal ganglia from 4 years of age (Figure 1D–F, K–M). Cerebellar atrophy with a predominance in the vermis was also progressive. White matter appeared stable and atrophy did not progress until the patient was 5 years old. Atrophy of the cerebrum and brainstem progressed rapidly after the age of 5 years (Figure 1G, N). The clinical and MRI findings were largely consistent with one another.

The patient's complete blood count and serum chemistry at the age of 3 years were all within normal ranges. Cerebrospinal fluid examination was also normal with respect to protein levels and cell count. Motor and sensory nerve conduction studies showed normal findings. Considering the patient's sensorineural hearing loss and leukodystrophy, we suspected a peroxisomal disorder and measured plasma VLCFA levels twice, at the ages of 3 and 4 years; however, VLCFA levels were almost normal (Table 1). Adrenocorticotropic hormone, cortisol, and arylsulfatase A levels were also normal.

To perform whole-exome sequencing, informed consent was obtained from the patient's guardians in accordance with the human study protocols approved by the institutional review boards at Sapporo Medical University Hospital and Hamamatsu University School of Medicine. We identified

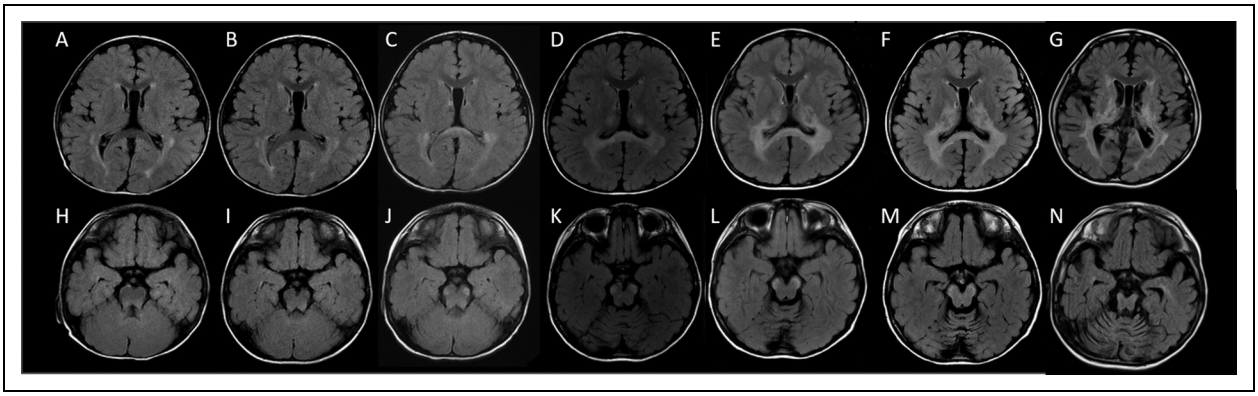

Fig. 1. Changes in brain MRI findings with age. Panels show axial images of fluid-attenuated inversion recovery (FLAIR) brain MRI from 1 year 8 months to 6 years 2 months of age. Images were obtained at 1 year 8 months (A and H), 2 years 11 months (B and I), 3 years 7 months (C and J), 4 years 1 month (D and K), 4 years 6 months (E and L), 5 years 1 month (F and M), and 6 years 2 months (G and N). White matter dystrophy was initially observed predominantly in the occipital lobe, and the lesion gradually spread to the corpus callosum ampulla, brainstem, and basal ganglia. Cerebral and cerebellar atrophy with a predominance in the vermis was also progressive with age.

Table 1. Plasma VLFCAs, phytanic acid, and pristanic acid levels

Peroxisomal metabolism product	Age at measurement (normal range)	
	3 years	4 years
Plasma VLFCAs		
C24:0/C22:0 ratio	0.816 (0.628–0.977)	0.825 (0.628–0.977)
C25:0/C22:0 ratio	0.022 (0.012–0.023)	0.020 (0.012–0.023)
C26:0/C22:0 ratio	0.006 (0.003–0.006)	0.007 (0.003–0.006)
Phytanic acid/I.S. ratio		1.262 (0.000–0.733)
Pristanic acid/I.S. ratio		0.202 (0.019–0.133)

VLCFAs; very long-chain fatty acids. I.S.; internal standard ^{13}C18:1 (1 μg/100 μL)

compound heterozygous variants in *HSD17B4* (NM_000414.4: c.[350A > T];[394C > T], p.[[Asp117Val]];[[Arg132Trp]]) in the patient. Sanger sequencing confirmed that the c.350A > T and c.394C > T variants were inherited from his father and mother, respectively (Supplemental Figure 1A, B). Both variants were extremely rare and predicted to be deleterious by *in silico* pathogenicity prediction tools (Supplemental Table S1). The c.394C > T variant had been previously identified in cases of DBP deficiency[2,4], but the c.350A > T variant was novel. Both missense variants were localized on the dehydrogenase unit (Supplemental Figure 1C).[1] According to the American College of Medical Genetics standards and guidelines, the variants were classified as likely pathogenic and uncertain significance, respectively (Supplemental Table S1). Importantly, the examination of peroxisomal metabolites revealed an increase in serum phytanic and pristanic acid levels (Table 1).[6] We therefore concluded that the clinical features of this patient were caused by type III DBP deficiency.

Discussion

Patients with DBP type I deficiency have deletions, insertions, and nonsense variants in *HSD17B4*, which produce truncated DBP, leading to the deficiency of both hydratase and dehydrogenase enzymes; such patients never live past 1 year of age. DBP type III deficiency is predominantly caused by *HSD17B4* missense variants that lead to the deficiency of dehydrogenase enzymes. Symptoms of DBP type III deficiency are often milder than those of type I, but most patients with missense variants also die within the first 2 years of life.[2] The symptoms of our case were milder than those of most patients, and he has survived for over 6 years. Ferdinandusse et al. hypothesized that the

Table 2. Clinical and genetic characteristics of DBP deficiency patients with progressive leukodystrophy in childhood

Reference	Soorani-Lunsing et al.[7]	Khan et al.[8]	Farkas et al.[9]	Landau et al.[10]	Present case
Age of reported patient (Y), Sex	8, Female	8, Male	6, Female	11.5, Female	6, Male
Sensorineural hearing loss (age at diagnosis)	+ (1Y2M)	+ (by 2Y)	n.d.	+ (2Y)	+ (moderate from neonatal period, worsened during infancy)
Regression (age when progressed)	+ (7Y)	+ (by 2Y)	+ (6Y)	+ (4Y)	+ (3Y)
MRI findings	Leukodystrophy posterior to anterior progression.	Leukodystrophy in the posterior deep white matter and pyramidal tract (2Y). Spread to cerebellum (3Y) and the anterior deep white matter (5Y).	Leukodystrophy posterior to anterior progression.	N (2Y) Diffuse abnormal signal in the basal ganglia and cerebral and cerebellar white matter (5Y).	T2-weighted hyperintensity in the posterior deep white matter and pyramidal tract (2Y). Spread to the thalamus and basal ganglia (4Y).
VLCFAs in plasma (age when measured)	↑ (1Y5M) ↑ (2Y1M) N (since 2Y1M)	↑ (1Y) N (3Y)	n.d.	N (5Y)	N (3Y) N (4Y)
Phytanic acid	N	N	n.d.	N	↑
Pristanic acid	N	N	n.d.	N	↑
HSD17B4 variants	c.311G>T, p.Arg104Met Homozygous	c.478G>C, p.Gly160Arg c.1717_1718delCT, p.Leu573Thrfs*3	c.936_937delTA, p.Thr313* c.1148A>G, p.Gln383Arg	c.868 + 1del G Intron 11 of 23 splicing	c.350A>T, p.Asp117Val c.394C>T, p.Arg132Trp

Y, year(s); M, month(s); MRI, magnetic resonance imaging; VLCFAs, very long chain fatty acids; N, within normal range; n.d., not determined.

effects of mutations on DBP protein structure may be associated with the severity of phenotypes.[2] Both of the missense variants identified in our patient were highly evolutionarily conserved and were located in the dehydrogenase unit, resulting in type III DBP deficiency (Supplemental Figure 1C). The Arg132 residue is buried at the dimerization surface of the dehydrogenase unit; a previous patient with a homozygous p.Arg132Trp alteration died before 36 months of age, indicating that mutations at this amino acid can have a strong impact on structural conformation.[2,4] Additionally, although the novel p.Asp117Val variant was predicted to be deleterious (Supplemental Table S1), its influence on protein structure and DBP activity remains unclear. However, biochemical analysis in our patient revealed the characteristic findings of DBP deficiency. A previous study suggested that the severity of clinical findings is likely affected by the degree of deficiency of DBP activity.[2] Considering these findings, we speculated that the p.(Asp117Val) variant might impair DBP enzyme activity, but that its functional impact is weaker than that of other missense variants.

Leukodystrophy in our patient progressed in the pyramidal tracts, including the occipital and cerebral peduncles, and then in the basal ganglia and thalamus. These patterns were similar to those in patients with X-linked adrenoleukodystrophy. In addition, cerebellar atrophy occurred at a relatively early stage in our patient, followed by both cerebral and brainstem atrophy. The brain MRIs of patients with DBP deficiency who survive long-term usually show cerebellar atrophy.[7–7] In our case, neurological regression and progressive leukodystrophy occurred in parallel; a strong association was observed between the progress of the MRI findings and neurological regression.

We identified four cases of DBP deficiency in the literature who also demonstrated progressive leukodystrophy in MRI in childhood (Table 2). None of these cases showed regression during infancy; regression and progressive MRI changes were observed in childhood, from 2 to 7 years of age. Sensory hearing loss was also observed in three of the four cases before 2 years of age, as in our patient.

The plasma VLCFA levels of two of these patients were slightly increased in the early infantile period but normalized with growth. In our patient, plasma VLCFA levels were normal at the ages of 3 and 4 years. Thus, VLCFA levels may normalize during childhood in patients with mild DBP deficiencies. In contrast, the levels of serum phytanic and pristanic acids, which are also peroxisomal metabolism products, were increased in our case; these levels were normal in the previous two patients with leukodystrophy. It should therefore be noted that even if VLCFA levels are normal, high levels of phytanic and pristanic acids may be an important finding that can lead to a diagnosis of peroxisomal disease, including DBP deficiencies.

Furthermore, because plasma VLCFA levels were within the normal range in our case and normalized during childhood in two previously reported patients with progressive leukodystrophy, it appears that plasma VLCFA levels are not associated with clinical course in such patients. These observations are consistent with findings from a study of DBP knockout mice in which severe chronic cerebral inflammation occurred, but was not associated with VLCFA levels.[11]

In conclusion, we report a male patient with type III DBP deficiency caused by compound heterozygous variants in *HSD17B4*. We suggest that DBP deficiency should be considered in patients with developmental regression and sensory hearing loss in childhood complicated by white matter dystrophy, even if VLCFAs are within normal levels.

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Author Contributions

AY, SF, YH, SM and ST contributed to conception, design, and analysis of information as well as drafting of manuscript with critical revision. MN, YK NS and HS contributed to conception, analysis of information, and critical revision of article. All authors gave final approval and agree to be accountable for all aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Trial Registration

Not applicable, because this article does not contain any clinical trials.

Supplemental Material

Supplemental material for this article is available online.

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