Table 1. continued

Patient	1	2	9	3	4	5	6	7	8	10	CRTR-D	BCAP31	X-ALD
Brain MRI	nd	T2 hyperintensities in periatrial WM, thin CC	T2 hyperintensities in GP, decreased volume WM, myelination delay, very thin CC; cerebellar vermian atrophy	T2 hyperintensities in BG, myelination delay, thin CC	Mild focal dilatation left Sylvian fissure, immature myelination	Myelination delay	No abnormalities	nd	Diffuse increased T1 hyperintensities in WM	Enlarged ventricles, thin CC, thin WM, myelination delay[e]	Myelination delay, T2 hyperintensities, thin CC, enlarged ventricles, cerebral/cerebellar atrophy	Periventricular hypomyelination, cerebral/cerebellar atrophy	Predominantly parieto-occipital WM abnormalities
Cerebral creatine (MRS)	nd	Deficient	Deficiënt	Deficient	nd	nd	nd	nd	nd	nd	Deficient	nd/normal[f]	nd
Adrenal	nd	nd	nd	nd	?	Small adrenal glands	nd	nd	nd	Adrenal hypoplasy	nd	nd	Addison's disease
Other symptoms				Episodes of high fever, hydronephrosis	Hydronephrosis					Thymus hypoplasia		Unexplained episodic fever	
Creatine uptake in fibroblasts	nd	Deficient	Deficient	Deficient	Deficient	Deficient	nd	nd	nd	nd	Deficient	nd	nd
Urinary Cr/Crn	Increased	Increased	Increased	Increased	nd	nd	nd	nd	nd	nd	Increased	nd	nd
VLCFAs	nd	Normal	Normal	Normal	Increased	Increased	Increased	Increased	Increased	Increased	nd	nd	Increased
Other biochemical abnormalities		Possible mitochondrial dysfunction[g], elevated NH_3 during febrile episodes		Possible mitochondrial dysfunction[g], elevated NH_3 during febrile episodes			Mildly elevated NH_3, normal lactate and organic acids				Possible mitochondrial dysfunction (rare)[h]		
Reference	Kamp et al. (1)	Anselm et al. (5), patient 1; Howidi et al. (8); Kamp et al. (1)	Osaka et al. (6)	Anselm et al. (5), patient 2		Corzo et al. (3), patient 3		Corzo et al. (3), patient 1	Corzo et al. (3), patient 2	Iwasa et al. (4)	Kamp et al. (1)	Cacciagli et al. (7)	Steinberg et al. (2)

BG, basal ganglia; CC, corpus callosum; Cr/Crn, creatine to creatinine ratio; CRTR-D, creatine transporter deficiency; FTT, failure to thrive; GI, gastro intestinal; GP, globus pallidus; IUGR , intrauterine growth retardation; LF, liver failure; MRI, magnetic resonance spectroscopy; MRS, magnetic resonance spectroscopy; nd, not determined; RF, respiratory failure; SD, standard deviations; SNHL, sensorineural hearing loss; VLCFAs, very long chain fatty acids; WM, white matter; X-ALD, X-linked adrenoleukodystrophy, ?, unknown; −, absent; +, present.

[a]One exceptional patient is alive at 13 years and attained sitting, with autonomous wheelchair and simple sign language.

[b]Normal audiogram at 4 years, mild low-frequency hearing loss at 36 years.

[c]Normal brain stem evoked potentials at 1 year.

[d]No consistent dysmorphisms were described.

[e]Brain autopsy showed in addition to heterotopia and dysplasia of inferior olivary nuclei.

[f]Normal creatine levels were measured in one patient.

[g]Transient elevated lactate, increased excretion tricarboxylic acid intermediates, ethyl-malonic acid and 3-methylglutaconic acid and/or decreased activity of respiratory chain complexes in muscle biopsy.

[h]Reported in one patient with a *SLC6A8* mutation.

is not described in isolated *ABCD1* (2) or *BCAP31* deficiencies (7). Only transient increases of liver transaminases, mainly during febrile episodes, were found in patients with *BCAP31–SLC6A8* deletions and were also described in patients with isolated *BCAP31* defects (7). Therefore, the hepatic cholestasis appears to result from the combined loss of *BCAP31* and *ABCD1*. Loss of *BCAP31* might aggravate the peroxisomal defect caused by *ABCD1* deficiency. BAP31 interacts with Fis1 (11), which, together with Dlp1, is implicated in both mitochondrial and peroxisomal fission (15). However, peroxisomes of normal size and number were reported in patients with *BCAP31–ABCD1* deletions (3, 4). Although the mechanism remains unclear, clearly there is a synergistic deleterious effect on bile acid transport and/or synthesis associated with concomitant BAP31 and ALD protein deficiency.

Severe dystonia and choreoathetosis were only noted in patients with *SLC6A8–BCAP31* deletions. However, dystonia is probably related to loss of *BCAP31* because it was also described in isolated *BCAP31* defects. Patients with *BCAP31–ABCD1* deletions died before these neurological symptoms usually appear.

Remarkably, patient 2 with an isolated deletion of the 3′-end exons of *SLC6A8* had the same severe phenotype as patients with *BCAP31* deficiency, but without the hearing loss. RT-PCR detected *BCAP31* mRNA in fibroblasts of this patient, which rules out a complete abrogation of *BCAP31* transcription; however, we did not rule out the possibility of an impaired transcription. It is unlikely that the severe phenotype is only due to the complete loss of *SLC6A8* because deletion of *SLC6A8* exons 5–12 was not associated with this severe presentation. If only deletions extending beyond the 3′-end of *SLC6A8* are associated with a more severe phenotype, then it is plausible that this phenotype is due to a perturbation of regulatory elements in the non-coding region between *SLC6A8* and *BCAP31*. Interestingly, one of the patients reported by Cacciagli et al. (7) had a deletion of *BCAP31* exon 8 to *SLC6A8* 3′-UTR. He had normal cerebral creatine levels but reduced fibroblast *SLC6A8* mRNA.

Three patients had contiguous gene deletions that extended beyond *SLC6A8*, *BCAP31* and *ABCD1*. These additional genes may also have contributed to their phenotype. Patient 10 had more profound microcephaly and more genes deleted than the other patients. *PLXNB3*, based on its abundant expression in the brain and role in neurite outgrowth, may contribute to cerebral features (16). In support of this, a patient with a deletion of *ABCD1* exons 3–10 and *PLXNB3* exons 1–2 had convulsions, predominantly occipital white matter abnormalities and possible developmental delay at 3 years (17). *PNCK* (deleted in patients 3 and 4) is also mainly expressed in the brain (18). No isolated defects of this gene have been reported to the best of our knowledge.

In conclusion, we confirm that *BCAP31* deficiency is associated with profound developmental delay, sensorineural hearing loss, failure to thrive, severe dystonia, increases of liver transaminases and childhood death. However, only deletions involving both *BCAP31* and *ABCD1* are associated with hepatic cholestasis and death in the first year, probably due to synergistic effects. Isolated deletions of *SLC6A8* extending beyond the 3′-end may be associated with a more severe phenotype than the classic CRTR-D, comparable to the phenotype in loss of *BCAP31* but without the hearing loss.

Supporting Information

The following Supporting information is available for this article:

Appendix S1. Data on direct sequencing of the break points and RT-PCR of *BCAP31*.

Additional Supporting information may be found in the online version of this article.

Acknowledgements

The authors are grateful to Vincent Lauffer, Warsha Kanhai, Lorna Pope, Ben Nota and Joe Ndika for their excellent laboratory assistance.

References

1. van de Kamp JM, Betsalel OT, Mercimek-Mahmutoglu S et al. Phenotype and genotype in 101 males with X-linked creatine transporter deficiency. J Med Genet 2013 Jul: 50 (7): 463–472.
2. Steinberg SJ, Moser AB, Raymond GV. X-linked adrenoleukodystrophy. In: RA P, Adams MP, Bird TD, eds. Online GeneReviews. 1999, revised April 2012.
3. Corzo D, Gibson W, Johnson K et al. Contiguous deletion of the X-linked adrenoleukodystrophy gene (ABCD1) and DXS1357E: a novel neonatal phenotype similar to peroxisomal biogenesis disorders. Am J Hum Genet 2002: 70 (6): 1520–1531.
4. Iwasa M, Yamagata T, Mizuguchi M et al. Contiguous ABCD1 DXS1357E deletion syndrome: report of an autopsy case. Neuropathology 2013: 33 (3): 292–298.
5. Anselm IA, Alkuraya FS, Salomons GS et al. X-linked creatine transporter defect: a report on two unrelated boys with a severe clinical phenotype. J Inherit Metab Dis 2006 Feb: 29 (1): 214–219.
6. Osaka H, Takagi A, Tsuyusaki Y et al. Contiguous deletion of SLC6A8 and BAP31 in a patient with severe dystonia and sensorineural deafness. Mol Genet Metab 2012: 106 (1): 43–47.
7. Cacciagli P, Sutera-Sardo J, Borges-Correia A et al. Mutations in BCAP31 cause a severe X-linked phenotype with deafness, dystonia, and central hypomyelination and disorganize the Golgi apparatus. Am J Hum Genet 2013: 93 (3): 579–586.
8. Howidi M, Parsons H. A case of creatine transporter deficiency in a young child with choreoathetosis. Curr Pediatr Res 2010: 14 (2): 102–105.
9. Ng FW, Nguyen M, Kwan T et al. p28 Bap31, a Bcl-2/Bcl-XL- and procaspase-8-associated protein in the endoplasmic reticulum. J Cell Biol 1997: 139 (2): 327–338.
10. Wang B, Heath-Engel H, Zhang D et al. BAP31 interacts with Sec61 translocons and promotes retrotranslocation of CFTRDeltaF508 via the derlin-1 complex. Cell 2008: 133 (6): 1080–1092.
11. Iwasawa R, Mahul-Mellier AL, Datler C, Pazarentzos E, Grimm S. Fis1 and Bap31 bridge the mitochondria-ER interface to establish a platform for apoptosis induction. EMBO J 2011: 30 (3): 556–568.
12. Breckenridge DG, Stojanovic M, Marcellus RC, Shore GC. Caspase cleavage product of BAP31 induces mitochondrial fission through endoplasmic reticulum calcium signals, enhancing cytochrome c release to the cytosol. J Cell Biol 2003: 160 (7): 1115–1127.
13. Wang B, Nguyen M, Breckenridge DG et al. Uncleaved BAP31 in association with A4 protein at the endoplasmic reticulum is an inhibitor of Fas-initiated release of cytochrome c from mitochondria. J Biol Chem 2003: 278 (16): 14461–14468.

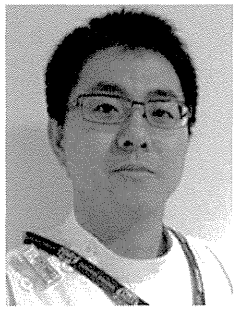
14. Ducret A, Nguyen M, Breckenridge DG, Shore GC. The resident endoplasmic reticulum protein, BAP31, associates with gamma-actin and myosin B heavy chain. Eur J Biochem 2003: 270 (2): 342–349.
15. Koch A, Yoon Y, Bonekamp NA, McNiven MA, Schrader M. A role for Fis1 in both mitochondrial and peroxisomal fission in mammalian cells. Mol Biol Cell 2005: 16: 5077–5086.
16. Hartwig C, Veske A, Krejcova S, Rosenberger G, Finckh U. Plexin B3 promotes neurite outgrowth, interacts homophilically, and interacts with Rin. BMC Neurosci 2005: 6: 53.
17. Matsumoto T, Miyake N, Watanabe Y et al. X-linked adrenoleukodystrophy with partial deletion of ALD due to fusion with the neighbor gene, PLXNB3. Am J Med Genet A 2005: 138A (3): 300–302.
18. Gardner HP, Rajan JV, Ha SI et al. Cloning, characterization, and chromosomal localization of Pnck, a Ca(2+)/calmodulin-dependent protein kinase. Genomics 2000: 63 (2): 279–288.

BRIEF COMMUNICATION

PIGO mutations in intractable epilepsy and severe developmental delay with mild elevation of alkaline phosphatase levels

*Kazuyuki Nakamura, †Hitoshi Osaka, ‡Yoshiko Murakami, †Rie Anzai, *Kiyomi Nishiyama, *Hirofumi Kodera, *Mitsuko Nakashima, *Yoshinori Tsurusaki, *Noriko Miyake, ‡Taroh Kinoshita, *Naomichi Matsumoto, and *Hirotomo Saitsu

Epilepsia, 55(2):e13–e17, 2014
doi: 10.1111/epi.12508



Kazuyuki Nakamura is a pediatric neurologist, and researches for epilepsy and brain malformation.

Summary

Aberrations in the glycosylphosphatidylinositol (GPI)–anchor biosynthesis pathway constitute a subclass of congenital disorders of glycosylation, and mutations in seven genes involved in this pathway have been identified. Among them, mutations in *PIGV* and *PIGO*, which are involved in the late stages of GPI-anchor synthesis, and *PGAP2*, which is involved in fatty-acid GPI-anchor remodeling, are all causative for hyperphosphatasia with mental retardation syndrome (HPMRS). Using whole exome sequencing, we identified novel compound heterozygous *PIGO* mutations (c.389C>A [p.Thr130Asn] and c.1288C>T [p.Gln430*]) in two siblings, one of them having epileptic encephalopathy. GPI-anchored proteins (CD16 and CD24) on blood granulocytes were slightly decreased compared with a control and his mother. Our patients lacked the characteristic features of HPMRS, such as facial dysmorphology (showing only a tented mouth) and hypoplasia of distal phalanges, and had only a mild elevation of serum alkaline phosphatase (ALP). Our findings therefore expand the clinical spectrum of GPI-anchor deficiencies involving *PIGO* mutations to include epileptic encephalopathy with mild elevation of ALP.

KEY WORDS: Congenital disorders of glycosylation, Epileptic encephalopathy, Glycosylphosphatidylinositol anchors, *PIGO*.

More than 100 mammalian cell-surface proteins are anchored to the plasma membrane by the addition of glycosylphosphatidylinositol (GPI) to their C-termini. More than 20 genes are involved in the GPI-anchor biosynthesis pathway[1,2] of which 7 are mutated in GPI-anchor deficiencies, a subclass of congenital glycosylation disorders, in association with neurologic impairments.[3–7] Among them, mutations in *PIGV*, *PIGO* (both are involved in the last step of GPI-anchor synthesis), and *PGAP2* (involved in fatty-acid GPI-anchor remodeling) have been identified in patients with hyperphosphatasia with mental retardation syndrome (HPMRS), also known as Mabry syndrome.[3–8]

PIGO encodes GPI ethanolamine phosphate transferase 3, which is also known as phosphatidylinositol-glycan biosynthesis class O. To date, only three HPMRS families with compound heterozygous mutations in *PIGO* have been reported. In this study, we performed whole exome sequencing of a Japanese family containing two affected siblings, one of them having epileptic encephalopathy, and identified novel *PIGO* mutations that expand the clinical spectrum of *PIGO* abnormalities to include epileptic encephalopathy.

Accepted November 6, 2013; Early View publication January 13, 2014.
*Department of Human Genetics, Yokohama City University Graduate School of Medicine, Yokohama, Japan; †Division of Neurology, Clinical Research Institute, Kanagawa Children's Medical Center, Yokohama, Japan; and ‡Research Institute for Microbial Diseases and World Premier International Immunology Frontier Research Center, Osaka University, Osaka, Japan

Address correspondence to Hirotomo Saitsu, Department of Human Genetics, Yokohama City University Graduate School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama 236-0004, Japan. E-mail: hsaitsu@yokohama-cu.ac.jp

Methods

DNA samples and subjects

All four family members (two affected siblings with epileptic encephalopathy and their parents) were analyzed. Clinical information, peripheral blood samples (individual II-1 and his parents), and the umbilical cord of individual II-2 were obtained after written informed consent was given. DNA was extracted using standard methods. Experimental protocols were approved by the institutional review board of Yokohama City University School of Medicine.

Whole exome sequencing (WES)

Genomic DNA was captured using the SureSelect Human All Exon v4 Kit (51 Mb; Agilent Technologies, Santa Clara, CA, U.S.A.) and sequenced on an Illumina HiSeq2000 (Illumina, San Diego, CA, U.S.A.) with 101 bp paired-end reads. Exome data processing, variant calling, and variant annotation were performed as previously described.[9] *PIGO* mutations detected by WES were confirmed by Sanger sequencing, and searched for in the variant database of our 408 in-house control exomes. For individual II-2, only those *PIGO* mutations identified in individual II-1 were checked by Sanger sequencing.

Flow cytometry

Surface expression of GPI-anchored proteins was examined as previously described.[8]

Results

Clinical features

A summary of the clinical features of individuals II-1 and II-2 is shown in Table S1. Both siblings had intractable seizures and severe developmental delay, which were compatible with epileptic encephalopathy.

Case report 1

Individual II-1 is a 19-year-old male born to nonconsanguineous parents after a 38-week gestation with no asphyxia. His birth weight was 3,250 g (+0.5 standard deviation [SD]), height 52.0 cm (−1.4 SD), and head circumference 34.0 cm (−0.5 SD). Developmental milestones were delayed with no head control achieved at 6 months. At 1 year of age, he developed complex partial seizures with staring, crying, and irregular respiration leading to cyanosis. Brain magnetic resonance imaging (MRI) revealed no abnormalities (Fig. 1A,B). At 1 year and 11 months of age, he had intractable seizures refractory to valproate, zonisamide, and clonazepam. His body weight at this time was 10.54 kg (−0.8 SD), height 84.8 cm (−0.1 SD), and head circumference 45.3 cm (−1.9 SD). He was able to smile but unable to control his head or speak any meaningful words. He had a high arched palate and a tented mouth (Fig. 1E). His muscle tone was hypotonic, and deep tendon reflexes were normal with negative Babinski sign. Chorea was observed mainly in the upper extremities. He did not show brachytelephalangy or nail aplasia (Fig. 1F).

Interictal electroencephalography (EEG), motor conduction velocities, visual evoked potential, short-latency somatosensory evoked potentials, and electroretinogram were normal. Auditory brain responses revealed only wave I. Serum alkaline phosphatase (ALP) levels were 436 U/L (normal range, 145–420),[10] and calcium and phosphate levels were normal. Metabolic analysis including lactate, pyruvate, very long fatty acids, and organic acid showed no abnormalities. His epileptic attacks sometimes led to generalized tonic–clonic seizures. Ictal EEG showed rhythmic fast waves, which appeared at the left side of the central sulcus, followed by diffuse irregular spikes and waves. Phenytoin and bromide treatment slightly decreased the seizure frequency. He was often admitted to the hospital (>40 times) with respiratory insufficiency following upper respiratory tract infection and/or prolonged convulsions, and initiated home oxygen therapy at 2 years of age.

Swallowing and hand movement gradually deteriorated, and spastic quadriplegia and hypertonus with rigidity of both upper and lower limbs appeared at 4 years of age. At 6 years of age, his condition gradually deteriorated, and a brain MRI at 6 years of age revealed diffuse cerebral and cerebellar atrophy (Fig. 1C,D). ALP was slightly elevated at around 10 years of age (900 U/L [normal range 130–560]), followed by a gradual decrease at around the age of 19 (300 U/L [normal range 65–260]). At this time he required mechanical ventilation. He had a very severe intellectual disability and partial seizures with dyspnea every day, despite administration of phenytoin, valproic acid, phenobarbital, bromide, clobazam, and nitrazepam. Pyridoxine has not been administered.

Case report 2

Individual II-2, the younger sister of individual II-1, was born without asphyxia. She did not show any facial dysmorphology or other congenital malformations. At 7 months of age, she developed generalized tonic–clonic seizures for which she was administered phenobarbital. At 1 year of age, she showed developmental delay with no head control. At this time, she was admitted to hospital due to epileptic convulsive status, and she died from multiorgan failure 3 days later. No autopsy was performed.

Identification of *PIGO* mutations and flow cytometry analysis

We filtered out variants registered in dbSNP135 data and our in-house 91 control exomes, and narrowed down 193 rare protein-altering and splice-site variants (Table S2). Among them, we identified compound heterozygous mutations in two genes: *PIGO* (GenBank accession number

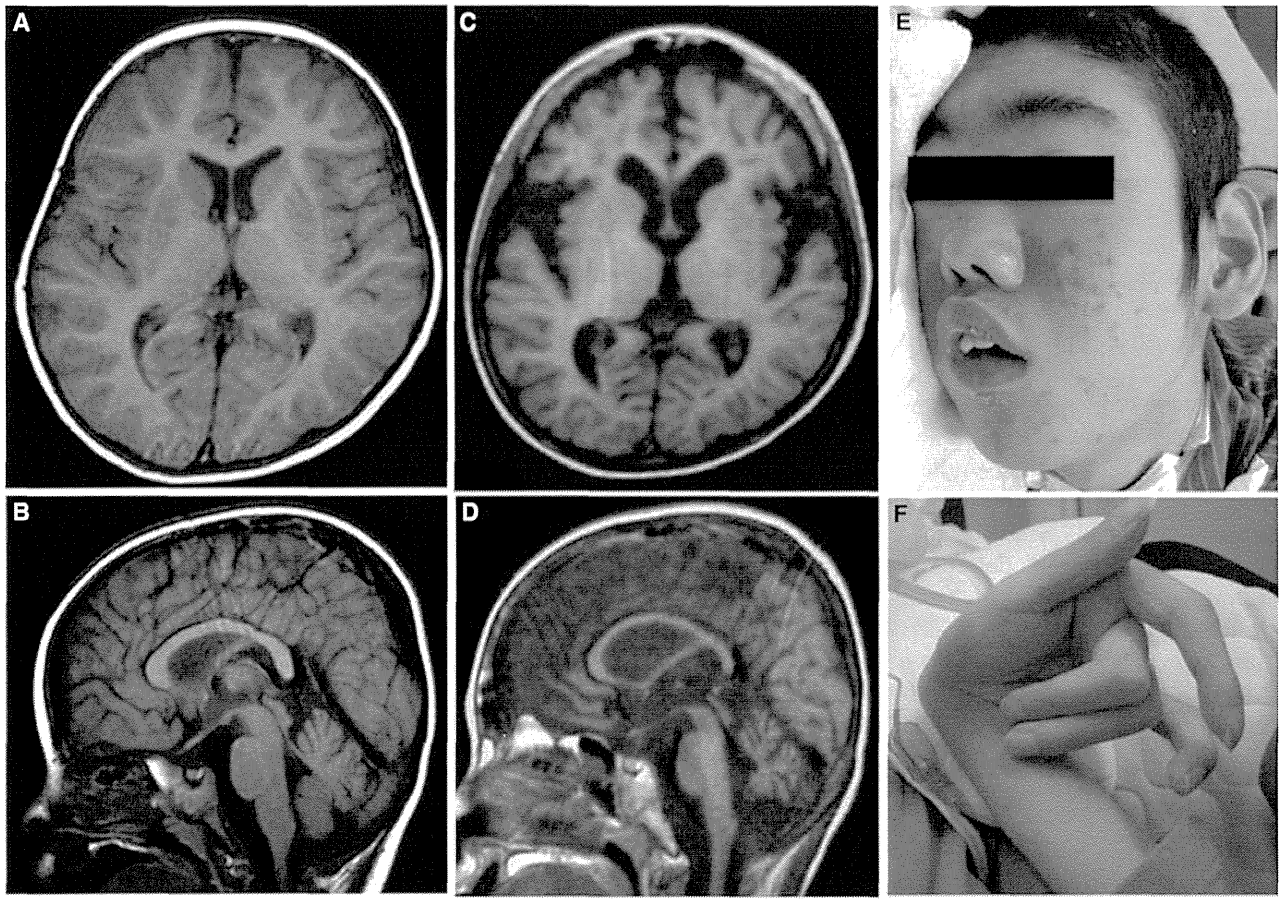


Figure 1.
T_1-weighted brain MRI of individual II-1. Axial (**A**) and sagittal (**B**) images revealed no signal or structural abnormalities at 1 year of age. Axial (**C**) and sagittal (**D**) images at 6 years of age showing diffuse cerebral and cerebellar atrophy. Facial (**E**) and hand (**F**) photographs of individual II-1 at 19 years of age showing tented mouth (**E**) and no anomalous fingers (**F**).

NM_032634.3) and *SCUBE1* (NM_173050.3) (Table S3). No homozygous mutation was detected. Four mutations are rare, but one of two mutations in *SCUBE1* is predicted as a polymorphism by web-prediction tools (Table S3). Therefore, *PIGO* mutations are the primary candidates. Two *PIGO* mutations were also found in his sister (individual II-2). A novel missense mutation c.389C>A (p.Thr130Asn) in exon 1 was inherited from their father and a novel nonsense mutation c.1288C>T (p.Gln430*) in exon 6 was inherited from their mother. Surface expressions of CD16 and CD24 on granulocytes from the individual II-1 were slightly, but clearly, decreased compared with a normal control and his mother, demonstrating GPI-anchor deficiencies in the patient (Fig. S1).

Discussion

In this study, we report two siblings with severe epileptic seizures, developmental delay, and mild elevation of ALP caused by two novel compound heterozygous mutations in *PIGO*. In individuals II-1 and II-2 of the present study, the p.Thr130Asn mutation in *PIGO* is located in an alkaline phosphatase–like core domain, whereas the p.Gln430* mutation is expected to produce a truncated protein that lacks most transmembrane domains (Fig. 2B). To date, only three families with HPRMS are reported in association with compound heterozygous *PIGO* mutations: p.Leu957Phe and p.Thr788Hisfs*5 in the first family, p.Leu957Phe and c.3069+5G>A skipping exon 9 leading to c.2855_3069del (p.Val952Aspfs*24) in the second,[5] and c.355C>T (p.Arg119Trp) and c.2497_2498del (p.Ala834Cysfs*131) in the third.[8] These five mutations led to markedly decreased expression of CD16, CD24, and CD59 on granulocytes from the patient or failed to recover expression of GPI-anchored proteins in *PIGO*-deficient CHO cells, suggesting that expression of GPI-anchored proteins was severely impaired in the patients.[5,8] On the other hand, individual II-1 with p.Thr130Asn and p.Gln430* mutations showed mildly decreased expression of CD16 and CD24 on the surface of blood granulocytes. This difference in the expression of GPI-anchored proteins might be associated with lacking characteristic features of HPMRS in individual

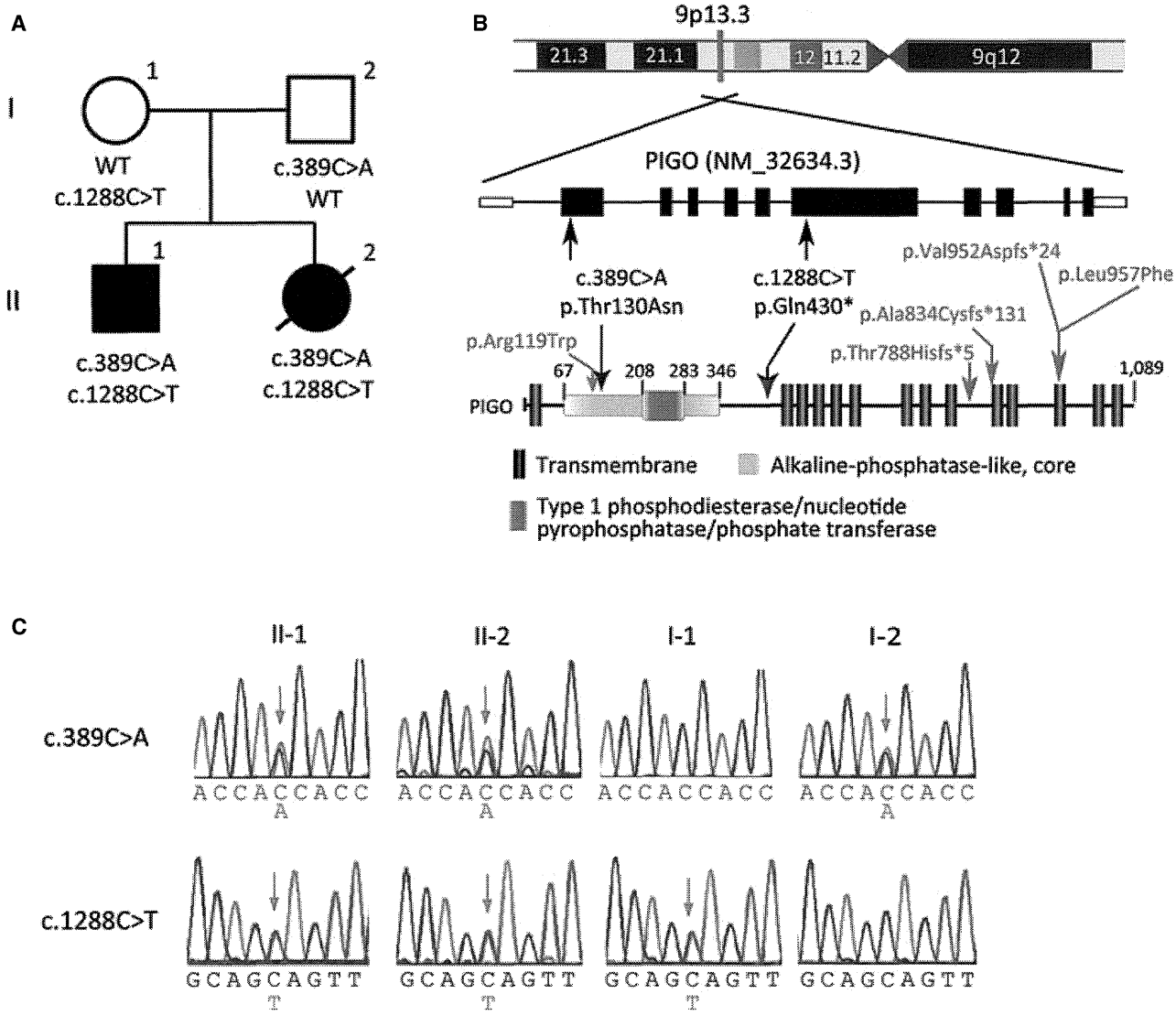


Figure 2.
(**A**) Familial pedigree of individuals I (II-1) and 2 (II-2). (**B**) Distribution of *PIGO* mutations. Previously reported mutations are highlighted in red. (**C**) Individuals II-1 and II-2 carrying compound heterozygous mutations in *PIGO*. Their mother (I-1) carried c.1288C>T (p.Gln430*), and their father (I-2) carried c.389C>A (p.Thr130Asn).

II-1, such as facial dysmorphic features, hypoplasia of distal phalanges, and elevation of serum ALP. Of interest, both patients in our report and a patient reported by Kuki et al. possessed missense mutations commonly in an alkaline phosphatase–like core domain, and showed progressive cerebral and cerebellar atrophy, and more severe intractable epilepsy and developmental delay than the other two families with *PIGO* mutations reported by Krawitz et al.[5,8] This fact raised a possibility that mutations in the alkaline phosphatase–like core domain can affect brain development and function more specifically regardless of expression of GPI-anchored proteins in blood granulocytes. Further accumulation of patients with *PIGO* mutations and functional analysis using neuronal cells are required for elucidating phenotype–genotype correlations in association with *PIGO* mutations.

Our data expand the clinical spectrum of GPI-anchor deficiencies to include epileptic encephalopathy. In addition, it has been recently reported that mutations in the *SLC35A2* encoding UDP-galactose transporter cause a congenital disorder of glycosylation in three patients, and five of them showed seizures with hypsarrhythmia pattern on electroencephalography.[11,12] Therefore, it is likely that abnormalities in glycosylation, including the GPI pathway, may be one of the underlying defects in epileptic encephalopathy.

In conclusion, we have described two siblings with epileptic encephalopathy that harbor novel compound

heterozygous mutations in *PIGO*. Further genetic analysis of GPI-anchor synthesis pathway is needed for the understanding of epileptic encephalopathy.

Acknowledgments

We would like to thank the patients and their families for their participation in this study. We thank Aya Narita and Nobuko Watanabe for technical assistance. This work was supported by the Ministry of Health, Labour and Welfare of Japan; a Grant-in-Aid for Scientific Research (A), (B), and (C) from the Japan Society for the Promotion of Science (A: 24249019, B: 25293085 25293235, C: 23590363); the Takeda Science Foundation; the Japan Science and Technology Agency; the Strategic Research Program for Brain Sciences (11105137); and a Grant-in-Aid for Scientific Research on Innovative Areas (Transcription Cycle, Exploring molecular basis for brain diseases based on personal genomics) from the Ministry of Education, Culture, Sports, Science and Technology of Japan (12024421, 25129705).

Disclosure

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. None of the authors has any conflicts of interest to disclose.

References

1. Kinoshita T, Fujita M, Maeda Y. Biosynthesis, remodelling and functions of mammalian GPI-anchored proteins: recent progress. *J Biochem* 2008;144:287–294.
2. Fujita M, Kinoshita T. GPI-anchor remodeling: potential functions of GPI-anchors in intracellular trafficking and membrane dynamics. *Biochim Biophys Acta* 2012;1821:1050–1058.
3. Freeze HH, Eklund EA, Ng BG, et al. Neurology of inherited glycosylation disorders. *Lancet Neurol* 2012;11:453–466.
4. Freeze HH. Understanding human glycosylation disorders: biochemistry leads the charge. *J Biol Chem* 2013;288:6936–6945.
5. Krawitz PM, Murakami Y, Hecht J, et al. Mutations in *PIGO*, a member of the GPI-anchor-synthesis pathway, cause hyperphosphatasia with mental retardation. *Am J Hum Genet* 2012;91:146–151.
6. Krawitz PM, Murakami Y, Riefl A, et al. *PGAP2* mutations, affecting the GPI-anchor-synthesis pathway, cause hyperphosphatasia with mental retardation syndrome. *Am J Hum Genet* 2013;92:584–589.
7. Hansen L, Tawamie H, Murakami Y, et al. Hypomorphic mutations in *PGAP2*, encoding a GPI-anchor-remodeling protein, cause autosomal-recessive intellectual disability. *Am J Hum Genet* 2013;92:575–583.
8. Kuki I, Takahashi Y, Okazaki S, et al. Vitamin B6-responsive epilepsy due to inherited GPI deficiency. *Neurology* 2013;81:1467–1469.
9. Saitsu H, Nishimura T, Muramatsu K, et al. *De novo* mutations in the autophagy gene *WDR45* cause static encephalopathy of childhood with neurodegeneration in adulthood. *Nat Genet* 2013;45:445–449.
10. Turan S, Topcu B, Gokce I, et al. Serum alkaline phosphatase levels in healthy children and evaluation of alkaline phosphatase z-scores in different types of rickets. *J Clin Res Pediatr Endocrinol* 2011;3:7–11.
11. Ng BG, Buckingham KJ, Raymond K, et al. Mosaicism of the UDP-galactose transporter *SLC35A2* causes a congenital disorder of glycosylation. *Am J Hum Genet* 2013;92:632–636.
12. Kodera H, Nakamura K, Osaka H, et al. *De novo* mutations in *SLC35A2* encoding a UDP-galactose transporter cause early-onset epileptic encephalopathy. *Hum Mutat* 2013;34:1708–1714.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Expression of GPI-anchored proteins on granulocytes from the patient.

Table S1. Clinical features of individuals with *PIGO* mutations.

Table S2. Summary of the exome sequencing performance.

Table S3. Candidate variants corresponding to the autosomal recessive model.

ELSEVIER

Brain & Development xxx (2014) xxx–xxx

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Case Report

A Japanese girl with an early-infantile onset vanishing white matter disease resembling Cree leukoencephalopathy

Kyoko Takano [a,b,*], Yu Tsuyusaki [a], Mutsumi Sato [a], Mariko Takagi [a], Rie Anzai [a], Mitsuko Okuda [a], Mizue Iai [a], Sumimasa Yamashita [a], Tetsuhiko Okabe [c], Noriko Aida [c], Yoshinori Tsurusaki [d], Hirotomo Saitsu [d], Naomichi Matsumoto [d], Hitoshi Osaka [a,e]

[a] *Division of Neurology, Kanagawa Children's Medical Center, Yokohama, Japan*
[b] *Department of Medical Genetics, Shinshu University School of Medicine, Matsumoto, Japan*
[c] *Department of Radiology, Kanagawa Children's Medical Center, Yokohama, Japan*
[d] *Human Genetics, Yokohama City University Graduate School of Medicine, Yokohama, Japan*
[e] *Department of Pediatrics, Jichi Medical School, Shimotsuke, Japan*

Received 14 August 2014; received in revised form 17 September 2014; accepted 1 October 2014

Abstract

Vanishing white matter disease (VWM)/childhood ataxia with central hypomyelination (CACH) is an autosomal recessive leukoencephalopathy caused by mutations in one of five genes, *EIF2B1–5*, encoding the 5 subunits of eukaryotic translation initiation factor 2B (eIF2B). The classical phenotype is characterized by early childhood onset and chronic progressive neurological deterioration with cerebellar ataxia, spasticity, optic atrophy and epilepsy. However, the onset of disease varies from antenatal period to adulthood. Cree leukoencephalopathy (CLE) is a severe variant of VWM and caused by a homozygous mutation (R195H) in the *EIF2B5* gene.

The patient reported in this study developed lethargy, vomiting and seizure 3 days after an oral poliovirus vaccination at the age of 4 months. She presented with rapid neurological deterioration within a month of onset. Brain MRI showed abnormal white matter intensity. Whole-exome sequencing identified two heterozygous mutations in the *EIF2B5* gene: a known mutation, c.584G>A (R195H, which is homozygous in CLE), and a novel mutation, c.1223T>C (I408T, which resides in the "I-patch"). Mutations in the "I-patch" encoded region of eIF2Bε may be related to an early-infantile onset phenotype. This patient exhibits an early-infantile onset and progressive disease course resembling CLE, suggesting a severe functional disruption of eIF2Bε caused by R195H as well as by I408T mutations.

Keywords: Vanishing white matter disease (VWM); Cree leukoencephalopathy; Eukaryotic translation initiation factor 2B; eIF2Bε; *EIF2B5*

1. Introduction

Vanishing white matter disease (VWM, OMIM# 603896)/childhood ataxia with central hypomyelination (CACH) is an autosomal recessive brain disorder showing white matter rarefaction and cystic degeneration. Neurological signs are dominated by progressive cerebellar ataxia, spasticity, optic atrophy and epilepsy. Febrile infections and minor head trauma may provoke rapid neurological deterioration following normal development [1]. Typical onset of VWM is at age 2–6 years, but varies from prenatal to adulthood. Patients with

* Corresponding author at: Department of Medical Genetics, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto, Nagano 3908621, Japan. Tel.: +81 263 37 2618; fax: +81 263 37 2619.
E-mail address: k_takano@shinshu-u.ac.jp (K. Takano).

http://dx.doi.org/10.1016/j.braindev.2014.10.002
0387-7604/

Please cite this article in press as: Takano K et al. A Japanese girl with an early-infantile onset vanishing white matter disease resembling Cree leukoencephalopathy.. Brain Dev (2014), http://dx.doi.org/10.1016/j.braindev.2014.10.002

early-infantile onset, especially before the age of 2 years, present with a severe phenotype that commonly leads to progressive deterioration and early death [1–3].

VWM is caused by mutations in any of the genes (*EIF2B1–EIF2B5*) encoding the 5 subunits (eIF2Bα–eIF2Bε) of the eukaryotic translation initiation factor 2B. The eIF2B complex has guanine nucleotide exchange factor (GEF) activity and is involved in the initiation of translation of mRNAs into polypeptides [4]. Dysregulation of protein synthesis under stress conditions exclusively affects glial cells (oligodendrocytes and astrocytes) in VWM brain [1]. Some genotype-phenotype correlations were identified in VWM patients [3]. In one example, Cree leukoencephalopathy (CLE), a fatal leukoencephalopathy observed in the Native American population, has a homozygous R195H mutation in the eIF2Bε. Its onset is between 3 and 9 months and death occurs by 2 years of age [5].

We report here a patient with an early-infantile onset VWM related to the *EIF2B5* gene. Her rapid neurological deterioration and findings of brain magnetic resonance imaging (MRI) was similar to those of CLE.

2. Case report

The patient is a 2 year-old girl, born to healthy and unrelated Japanese parents at term and uneventfully. The family history was negative for neurological disorders. She developed lethargy, vomiting and seizures without a febrile illness 3 days after an oral poliovirus vaccination at the age of 4 months. She was referred to our medical center because of intractable seizures at the age of 5 months. Her height was 65 cm (+0.2 SD), her weight was 5.72 kg (−1.6 SD), and her head circumference was 39.1 cm (−2.2 SD). Although her developmental milestones were mildly delayed, she could hold her head, smile, follow objects with eyes and suckle during the interictal period. She experienced several status epilepticus and refractory complex-partial seizures. She was treated with an intravenous midazolam for a month followed by high-dose phenobarbital and other oral antiepileptic drugs. Brain MRI showed a diffuse bilateral symmetrical abnormal signal of the deep white matter characterized by a T2-weighted hyperintensity and fluid-attenuated inversion-recovery (FLAIR) hypointensity (Fig. 1A and B). Thus, the patient had a leukoencephalopathy without macrocephaly, and an initial diagnosis of either VWM, Krabbe disease, or metachromatic leukodystrophy was suspected because of her brain MRI findings. The latter two diagnoses were excluded via the following investigations. Blood tests for metabolic disorders were normal, including: the levels of lactate, very long-chain fatty acids, the activities of lysosomal enzymes (galactocerebrosidase and arylsulfatase A), and amino acid analysis. Cerebrospinal fluid (CSF) analysis showed an elevation of protein (109 mg/dL; normal range 10–45 mg/dL) and glycine (21.0 nmol/mL; normal range 3–8 nmol/mL). The ratio of CSF to plasma glycine was slightly elevated (0.053; normal range < 0.04). Interictal electroencephalograph (EEG) did not show epileptic discharges. She presented with rapid neurological deterioration, loss of head control, axial hypotonia, spasticity with increased deep tendon reflexes and clonus, sluggish light reflex and dysphagia within a month of onset. EEG exhibited high voltage multifocal spikes.

To identify the genetic cause of this early-infantile onset leukoencephalopathy without macrocephaly, we performed whole-exome sequencing as described previously [6]. The institution's ethnical committee approved this study. Peripheral blood samples were obtained from the patient and parents after informed consent was obtained. Compound heterozygous mutations in *EIF2B5* were detected in the patient. The first mutation transmitted from her father was c.584G>A in exon 4, resulting in the replacement of an arginine residue by histidine (R195H). The second mutation, inherited from her mother, was a novel c.1223T>C in exon 8, resulting in the replacement of an isoleucine residue by threonine (I408T). Both mutations were not found in 212 normal Japanese control exomes.

Now, the patient is 25 months old. Follow-up brain MRI revealed progressive expansion of the white matter lesion with involvement of thalami and the globus pallidus (Fig. 1C–F), where the lesion signal intensity is the same as that of CSF (Fig. 1E and F). She is bedridden, spastic quadriplegic, hardly ever reacts to stimuli and presents with shallow breathing. She has suffered from aspiration pneumonia and needed non-invasive positive pressure ventilation several times. She depends on home oxygen therapy and nasoduodenal feeding due to swallowing difficulty and gastroesophageal reflux. Her EEG still exhibits high voltage multifocal spikes, but apparent seizures are not observed.

3. Discussion

Brain MRI findings and mild elevation of glycine in CSF were consistent with those of VWM [1]. However, her presentation with an early-infantile onset at the age of 4 months and rapid deterioration following a vaccination instead of a febrile illness or mild head trauma, were not typical of VWM. To date, one VWM patient has been reported with apparent developmental delay and hypotonia shortly after a vaccination and an upper respiratory tract infection at the age of 5 months [2]. Thus, we suspect that vaccinations are involved in the onset of VWM.

The homozygous R195H mutation in the *EIF2B5* gene has been associated with a severe variant of VWM: Cree leukoencephalopathy (CLE). Our patient has compound heterozygous mutations again consisting

Please cite this article in press as: Takano K et al. A Japanese girl with an early-infantile onset vanishing white matter disease resembling Cree leukoencephalopathy.. Brain Dev (2014), http://dx.doi.org/10.1016/j.braindev.2014.10.002

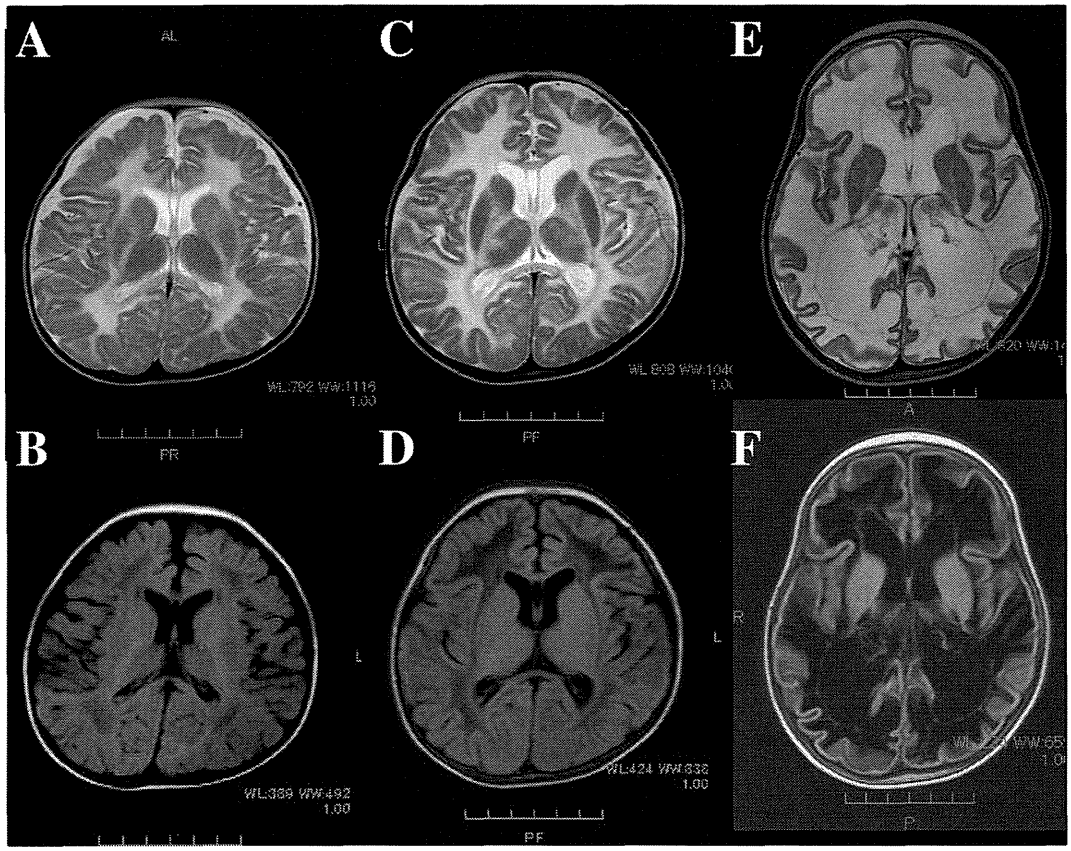


Fig. 1. Axial T2-weighted (A, C, E) and FLAIR (B, D, F) images of the patient. The first brain MRI at the ages of 5 months shows diffuse bilateral symmetrical abnormal intensity of the deep white matter (A and B). Images obtained 3 months later exhibits expansion of the white matter lesion with involvement of part of the thalami and the globus pallidus (C and D). The latest images obtained at the age of 25 months shows that whole white matter has abnormal intensity, similar to cerebrospinal fluid, indicating cystic degeneration and the thalami and the globus pallidus are totally involved (E and F). Brain atrophy is not observed.

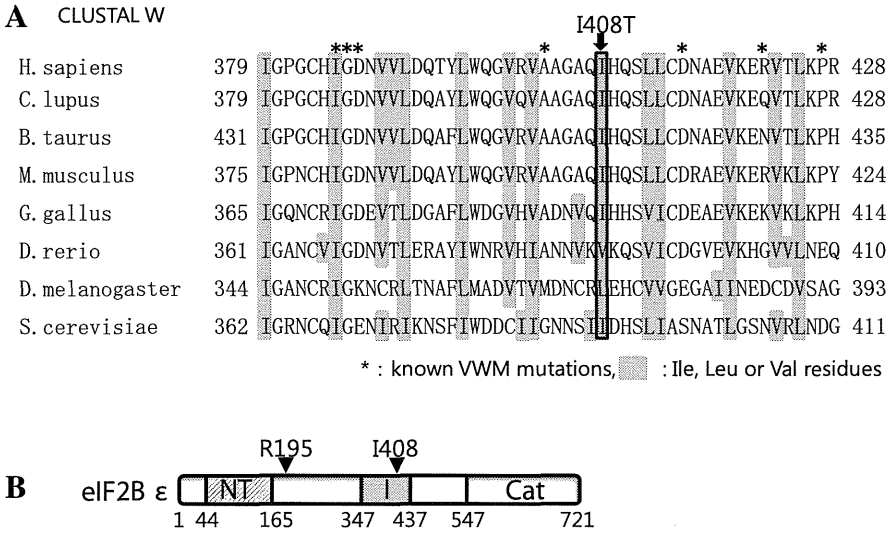


Fig. 2. Sequence alignment of eIF2Bε homologs (A) and structure of human eIF2Bε (B). An arrow shows the location of I408T mutation. Shadowed amino acids indicate isoleucine, leucine and valine residues. Asterisks denote known mutations causing VWM in the literature (A). Arrowheads indicate the location of patient's mutations (B). Abbreviations: nucleotidyl transferase domain (NT), I-patch (I), catalytic domain (Cat).

Please cite this article in press as: Takano K et al. A Japanese girl with an early-infantile onset vanishing white matter disease resembling Cree leukoencephalopathy.. Brain Dev (2014), http://dx.doi.org/10.1016/j.braindev.2014.10.002

Table 1
Patients with mutations in "I-patch" in eIF2Bε.

Mutation in I-patch	2nd mutation	Age at disease onset (years)	Age at last examination (years)	Score of disability[a]	Refs.
I408T	R195H	0.3	2.1	4	[b]
V430A	S447L	0.4	0.6	5	[2]
P427L	P323S	0.8	1	5	[3]
L425R	R113H	1	3	4	[3]
I385V	Y343C	1	4	5	[3]
D387G	R113H	1.5	8	4	[3]
A403V	R113H	1.5	2.3	Not available	[10]
D387G	R113H	2	6	5	[3]
P427L	Homozygous	2	8	2	[8]
N376D	S447L	2.9	5	2	[11]
I385V	Y343C	3	7	3	[3]
R422X	R113H	3	8.5	3	[3]
G386V	S610-D613del	4.5	5.9	2	[11]
Average		1.8	–	3.7	

[a] Score of disability (Fogli et al. [3]): 1, stiff gait; 2, walk with help; 3, wheelchair-bound; 4, help for daily living; 5, death.
[b] This case.

of R195H and a novel I408T in the *EIF2B5* gene, and also has an early-infantile onset VWM that closely resembles CLE with respect to the onset, the progressive disease course and the brain MRI showing involvement of the thalami and globus pallidus [7]. However, her early-infantile onset phenotype cannot be explained by the R195H mutation alone, because other patients that have R195H-containing compound heterozygous mutations, either R195H/R113H or R195H/Y483C, presented with classical or adult-onset phenotypes of VWM, respectively [3,8]. The novel I408T mutation is expected to be pathogenic, because isoleucine at position 408 is highly evolutionally conserved across different species (Fig. 2A). Moreover, this amino acid change is predicted to be deleterious by SIFT (http://sift.jcvi.org/), PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/index.shtml) and Mutation Taster (http://www.mutationtaster.org/). The isoleucine residue at position 408 resides in the "I-patch", which is a loose hexad repeat, mainly composed of isoleucine, leucine or valine residues (Fig. 2A and B). This has been reported to be involved in interactions between the catalytic eIF2Bγε complex and the other α, β and δ subunits of the complete eIF2B complex [9]. Thus, the I408T mutation may exert an adverse effect on the function of the eIF2B complex. In addition, Table 1 shows 13 patients with mutations in the "I-patch" encoded region of eIF2Bε. They presented with an early mean age of onset of 1.8 years (range, 0.3–5.9 years) and their score of disability is relatively high. This suggests that such "I-patch" mutations may be correlated with an early-infantile onset form.

In summary, the patient presented with an early-infantile onset phenotype as well as a progressive disease course resembling CLE, suggesting a severe functional distortion of the eIF2Bε protein caused by a compound heterozygous mutation of R195H and I408T of paternal and maternal origin, respectively.

Acknowledgments

We would like to express our gratitude to the patient and family for their participation in this study. We would like to thank to Dr. Toya Ohashi for assays of lysosomal enzyme activity.

References

[1] van der Knaap MS, Pronk JC, Scheper GC. Vanishing white matter disease. Lancet Neurol 2006;5:413–23.
[2] van der Knaap MS, van Berkel CG, Herms J, van Coster R, Baethmann M, Naidu S, et al. EIF2B-related disorders: antenatal onset and involvement of multiple organs. Am J Hum Genet 2003;73:1199–207.
[3] Fogli A, Schiffmann R, Bertini E, Ughetto S, Combes P, Eymard-Pierre E, et al. The effect of genotype on the natural history of eIF2B-related leukodystrophies. Neurology 2004;62:1509–17.
[4] Scheper GC, Proud CG, van der Knaap MS. Defective translation initiation causes vanishing of cerebral white matter. Trends Mol Med 2006;12:159–66.
[5] Fogli A, Wong K, Eymard-Pierre E, Wenger J, Bouffard JP, Goldin E, et al. Cree leukoencephalopathy and CACH/VWM disease are allelic at the EIF2B5 locus. Ann Neurol 2002;52:506–10.
[6] Saitsu H, Nishimura T, Muramatsu K, Kodera H, Kumada S, Sugai K, et al. De novo mutations in the autophagy gene WDR45 cause static encephalopathy of childhood with neurodegeneration in adulthood. Nat Genet 2013;45:445–9.
[7] Harder S, Gourgaris A, Frangou E, Hopp K, Huntsman R, Lowry N, et al. Clinical and neuroimaging findings of Cree leukodystrophy: a retrospective case series. AJNR Am J Neuroradiol 2010;31:1418–23.

Please cite this article in press as: Takano K et al. A Japanese girl with an early-infantile onset vanishing white matter disease resembling Cree leukoencephalopathy.. Brain Dev (2014), http://dx.doi.org/10.1016/j.braindev.2014.10.002

[8] Horzinski L, Huyghe A, Cardoso MC, Gonthier C, Ouchchane L, Schiffmann R, et al. Eukaryotic initiation factor 2B (eIF2B) GEF activity as a diagnostic tool for EIF2B-related disorders. PLoS One 2009;4:e8318.

[9] Wang X, Wortham NC, Liu R, Proud CG. Identification of residues that underpin interactions within the eukaryotic initiation factor (eIF2) 2B complex. J Biol Chem 2012;287:8263–74.

[10] van der Lei HD, Steenweg ME, Barkhof F, de Grauw T, d'Hooghe M, Morton R, et al. Characteristics of early MRI in children and adolescents with vanishing white matter. Neuropediatrics 2012;43:22–6.

[11] Wu Y, Pan Y, Du L, Wang J, Gu Q, Gao Z, et al. Identification of novel EIF2B mutations in Chinese patients with vanishing white matter disease. J Hum Genet 2009;54:74–7.

Please cite this article in press as: Takano K et al. A Japanese girl with an early-infantile onset vanishing white matter disease resembling Cree leukoencephalopathy.. Brain Dev (2014), http://dx.doi.org/10.1016/j.braindev.2014.10.002

別冊日本臨牀　新領域別症候群シリーズ　No. 29（2014年9月20日発行）別刷

神経症候群（第2版）

—その他の神経疾患を含めて—

IV

VIII　先天異常/先天奇形

破壊性獲得性二次性障害

大脳萎縮症

小坂　仁

破壊性獲得性二次性障害

大脳萎縮症

Cerebral atrophy

小坂　仁

Key words：アポトーシス，ネクローシス，白質，灰白質

1. 概念・定義

大脳が形成された後の何らかの破壊，萎縮による細胞死による大脳萎縮．

2. 疫　　学

我が国における大規模な調査はなく不明である．

3. 病　　因[1-3]

1）出生前の異常

a. 母体環境によるもの

a）母体疾患によるもの

妊娠中毒症，糖尿病，甲状腺疾患，高血圧，膠原病などは，胎盤機能不全などを通じて大脳萎縮を生じさせる可能性がある．

b）薬剤による影響

向精神薬，抗痙攣薬，アルコール，麻薬，麻酔薬など

b. 胎内感染

トキソプラズマ，風疹ウイルス，サイトメガロウイルス，単純ヘルペスウイルス感染など

c. 染色体異常，代謝性疾患などの遺伝子異常による疾患

2）周産期異常

仮死，血管障害，分娩外傷など

3）出生後の異常

(1) 代謝異常などの遺伝子異常による疾患

(2) 感染，脳症，脳血管障害，外傷など後天性疾患

4. 病　　態[1]

中枢神経系の構成細胞であるニューロン，オリゴデンドロサイト，アストロサイトなどに，不可逆的な細胞傷害が起き，細胞死が起こることによる萎縮性変化が基本病態である．未熟な細胞に生じる障害は成人期と異なる反応を示す．細胞死の分子機構を図1に示す．

細胞死には，従来顕微鏡学的に細胞膜が消失し，細胞内小器官が浮腫し，空胞化しタンパク分解酵素やDNA分解酵素が活性化しクロマチンが無秩序に分解されDNAがスメア様に分解を受けるネクローシスおよび，ATPを用い，分解酵素のカスパーゼによって担われ，DNAがラダー状に分解を受ける細胞死であるアポトーシスが知られている．新生児低酸素性虚血性障害の研究などより，アポトーシスとネクローシスは厳密に区別されるものではなく，一連の反応であることがわかっている．

5. 診断と鑑別診断(表1)[1-5]

遺伝性疾患には非常に多くの鑑別診断が存在するため，MRIにより画像的に病変の主体が灰白質(ニューロン)か白質(オリゴデンドロサイトなど)で分類し，灰白質も，皮質，深部灰白質に分け，白質も皮質下白質，深部白質かで分け分類する．また病変が，髄鞘化不全によるものはこれらから鑑別し，臨床・検査所見から原因診断に至る．

Hitoshi Osaka: Department of Pediatrics, Jichi Medical School　自治医科大学 小児科学

0047-1852/14/¥60/頁/JCOPY

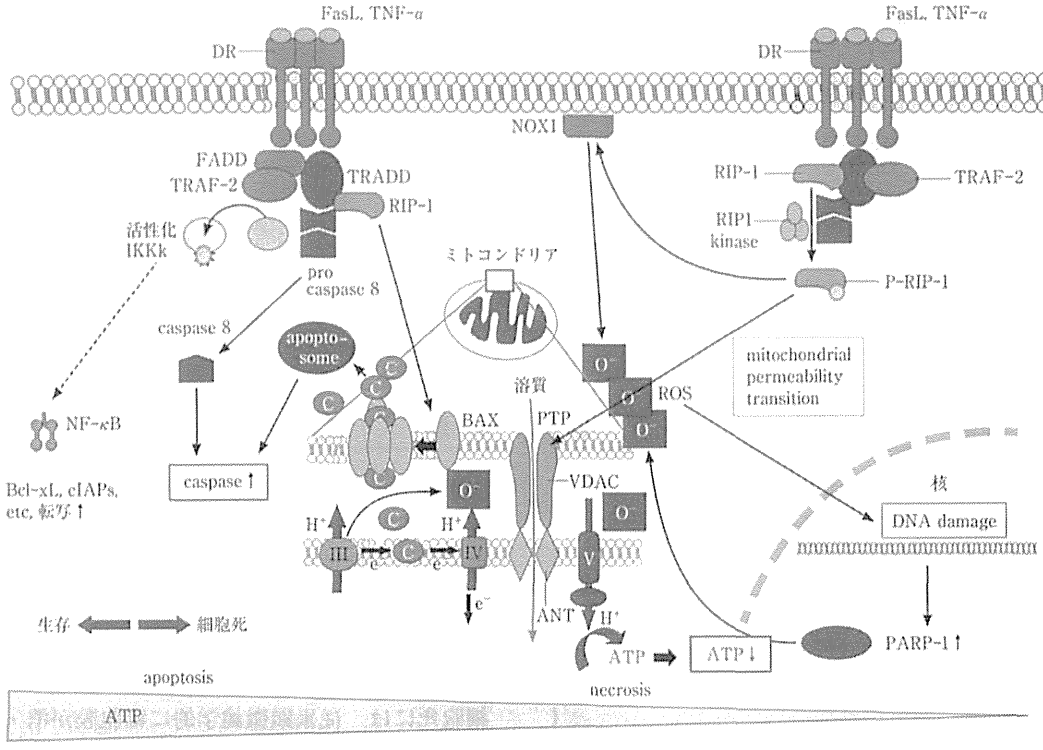


図1　様々な細胞死と生存(文献[1]より引用)

Fasリガンド(FasL), tumor necrosis factor(TNF)-αといった，細胞死誘導作用のあるサイトカインがTNF受容体superfamily(death receptors: DR)に結合すると，受容体は，3量体になる．この3量体はFAS-associated protein with death domain(FADD), TNFR-associated factor(TRAF)-2, receptor interacting protein(RIP)-1, TNFR-associated death domain(TRADD)などと複合体を形成する．

生存状態：(図の左端)十分にATPのある状況では，IκB kinase(IKKk)のリン酸化が起き，nuclear factor-κB(NF-κB)の核内誘導を起こしB-cell lymphoma-extra-large(Bcl-xL), inhibitors of apoptosis(cIAPs)などの，アポトーシス阻害に働くタンパクの転写誘導を促す．

アポトーシス：(図の左側)ATPの低下状態では，RIP-1により，pro caspase 8が分解され，下流のカスパーゼを活性化し(外来性経路)あるいはBaxがミトコンドリア外膜に4量体のチャンネルを形成し，cytochrome C(C)が細胞質に流入，procaspase-9などとapoptosomeを形成しさらにカスパーゼシグナルを増強させる．

ネクローシス：(図の右半分)さらにATPが低下した状態においては，RIP1キナーゼの作用下，NADPH oxidase(NOX1)がreactive oxygen species(ROS)を生成し，さらにはvoltage depedent anion channel(VDAC), adenine nucleotide transporter(ANT)などからなるmitochondrial transition pore(PTP)を開口させmitochondria, permeability transitionにより細胞内溶質がミトコンドリア内に流入し，浮腫を起こす(programmed necrosis)．最もATP枯渇の状況ではDNAダメージが通常は，DNA修復に働くpoly ADP-ribose polymerase-1(PARP-1)の強い活性化により，ミトコンドリアのプロトン勾配を破壊し，ATPのさらなる枯渇を招き，活性化酸素の上昇を招きそれがDNA障害をさらに強める．

6. 治療と予後

多くは，対症療法となる．白質病変は筋緊張亢進に至る場合が多く筋弛緩剤が用いられる．深部灰白質病変では，不随意運動を伴うことが多いため不随意運動緩和薬，皮質灰白質病変ではてんかんを伴うことが多いため，抗てんかん薬が用いられる．

また原因治療が可能な疾患(表1で#のついた疾患)では，速やかに治療を開始するとともに，原因確定以前でも診断的治療を行うことも考慮する．

予後は，疾患により異なる．

表1 大脳萎縮症(遺伝性)の分類

白質病変が主体の疾患

1. 深部白質から病変が始まる疾患

a. 異染性白質ジストロフィー症
(アリルスルファターゼAやスフィンゴリピド活性化タンパクB異常による，スルファチドの蓄積)
b. クラッベ病 #(一部で骨髄移植)
(ガラクトシルセラミダーゼ活性低下によりガラクトシルセラミドが蓄積)
c. 副腎白質ジストロフィー #(早期の骨髄移植)
(ペルオキシゾームのトランスポーター異常による極長鎖脂肪酸分解阻害)
d. vanishing white matter型白質脳症
(EIF2B1-5異常により，ストレスに際してタンパク合成を停止する小胞体ストレスの不全)
e. 巨大軸索ニューロパチー
(中間型フィラメントの構造異常)
f. *フェニルケトン尿症 #(食事療法)
(フェニルアラニン水酸化酵素活性低下による)
g. *メープルシロップ尿症 #(食事療法)
(分枝鎖アミノ酸α-ケト酸脱水素酵素複合体の異常)
h. *ホモシステイン尿症 #(葉酸，ビタミンB_6)
(シスタチオニンβ合成酵素異常)
i. 5,10メチレンテトラヒドロ葉酸還元酵素欠損 #(ベタイン，コバラミン，葉酸)
(尿中ホモシスチンと血中のメチオニンが低値)
j. コバラミン代謝異常 #(コバラミン)
(iに加えメチルマロン酸尿症を伴う)
k. ビオチニダーゼ欠損症 #(ビオチン)
(ビオチンの生成不全のビオチニダーゼ欠損症とホロカルボキシラーゼ欠損症からなる)
l. メチオニンSアデノシルトランスフェラーゼ欠損症
(高メチオニン血症をきたす)
m. Lowe症候群
(phosphatidylinositol-4,5-biphosphate-5 phosphatase欠損による，ゴルジ輸送系異常)
n. メロシン欠損性先天性筋ジストロフィー症
(lamina-α-2異常)
o. ムコリピドーシスIV型
(mucolipin-1異常により，カルシウム輸送およびライソゾーム輸送系異常をきたす)
p. 脳梁低形成を伴う劣性痙性対麻痺 spatacsin(SPG11)およびspatizin(SPG15)
q. シェーグレン・ラーソン症候群
(fatty aldehyde dehydrogenase欠損，ALDH3A2遺伝子他複数の遺伝子が関与)

2. 皮質下白質に脱髄の主座をもつ疾患

a. 皮質下嚢胞を伴う巨脳白質脳症
(MLC1あるいはHEPACAM異常，いずれも機能不明)
b. Aicardi-Goutières syndrome(アイカルディ・グティエール症候群)
(DNA修復に関わる遺伝子異常)
c. コケイン症候群
(DNA修復障害)
d. *ガラクトース血症 #(乳糖制限)
(ガラクトース代謝に関わる酵素欠損による)

3. 髄鞘化不全による疾患

a. ペリツェウス・メルツバッヘル病
(proteolipid protein 1の異常)
b. ペリツェウス・メルツバッヘル様病1
(gap junction proteinの異常)
c. 基底核および小脳萎縮を伴う髄鞘形成不全症
(チュブリンTUBB4Aの異常による)

(次頁につづく)

（表1つづき）

d. 18q−症候群
（ミエリン塩基性タンパクの欠失が原因）
e. アラン・ハーンドン・ダドリー症候群
（monocarboxylic acid transporter 8欠損による甲状腺ホルモン膜輸送障害）
f. サラ病
（SLC17A5異常によるライソゾームへのシアル酸蓄積）
g. 小脳萎縮と脳梁低形成を伴うびまん性大脳白質形成不全症
（RNA polymerase IIIをコードするPOLR3AおよびPOLR3B異常）
h. 先天性白内障を伴う髄鞘形成不全症
（FAM126A(DRCTNNB1A)異常によるオリゴデンドロサイトの分化への関与が示唆）
i. 失調，歯牙低形成を伴う髄鞘形成不全症
（RNA polymerase IIIのサブユニットをコードするPOLR3A遺伝子の異常）
j. 脱髄型末梢神経炎，中枢性髄鞘形成不全症，Waardenburg症候群，Hirschsprung病
（SOX10異常による神経堤由来細胞の発生異常）
4. 種々の白質病変を取りうる疾患
a. 非ケトーシス型グリシン血症
（グリシン開裂系異常による高グリシン血症）
b. ジヒドロピリミジン脱水素酵素欠損症
（ウラシルとチミンの代謝酵素．尿中チミンとウラシルが上昇するピリミジン代謝異常症）
c. 3−ヒドロキシ−3−メチルグルタリル補酵素Aリアーゼ欠損症
（ロイシンと脂肪酸代謝に関わる．有機酸代謝異常）

灰白質が主体の疾患
1. 深部灰白質が主
a. パントテン酸キナーゼ関連神経病(ハラーホルデン・スパッツ病)
（パントテン酸キナーゼ2異常により鉄の貯留が起こる）
b. 若年性ハンチントン舞踏病
（ハンチンチンのCAGリピート延長）
c. イソ吉草酸血症　#(L−カルニチン，ロイシン制限)
（イソバレリルCoA脱水素酵素異常によるイソバレリン酸貯留）
d. コハク酸セミアルデヒド脱水素酵素欠損症
（GABAと4−hydroxybutyric acidが蓄積）
e. クレアチン欠損症　#(一部でクレアチン，オルニチン投与)
（クレアチン合成酵素もしくはクレアチントランスポーター異常）
2. 皮質が主たる病変の疾患
a. 神経セロイドリポフスチン症
（*CLN1*～*CLN8*など複数遺伝子関与，一部はアポトーシスに関わる）
b. ニーマン・ピック病　#(C型でミグルスタット投与)
c. レット症候群
（転写因子MECP2異常）
d. アルパース症候群
（ミトコンドリアDNAポリメラーゼ異常による）
e. 乳児神経軸索ジストロフィー
（ホスホリパーゼA2欠損により，神経軸索にスフェロイド形成が起こる）
f. アスパルチルグルコサミン尿症
（アスパルチルグルコサミナーゼ異常によるオリゴ糖症）

皮質灰白質と白質が障害される疾患
1. 深部灰白質は保たれるもの
a. アルパース病

（次頁につづく）

(表1つづき)

b. メンケス病
c. ムコ多糖症
d. 脂質蓄積症
e. ペルオキシソーム病

深部灰白質と白質が傷害される疾患
1. 視床病変が強い疾患
a. クラッベ病
b. GM1ガングリオシドーシス
(β-ガラクトシダーゼ)
c. GM2ガングリオシドーシス
(β-ヘキソサミニダーゼA, B)
d. ウィルソン病 #(銅キレート剤)
(ATP7B異常による血中, 胆汁中への銅の排泄異常)
2. 淡蒼球病変が強い疾患
a. カナバン病
(アスパルトアシラーゼ欠損によりアスパラギンと酢酸が減少し, ミエリンタンパク合成低下)
b. カーンズ・セイヤー症候群
(ミトコンドリアDNAの粗大欠失や重複による)
c. メチルマロン酸血症 #(ビタミン B_{12} 投与)
(メチルマロニルCoAムターゼ異常あるいは補酵素のビタミン B_{12} の利用異常)
d. *メープルシロップ尿症
e. L-2-ヒドロキシグルタル酸尿症
(L-2-ヒドロキシグルタル酸分解酵素異常)
f. フコシドーシス
(α-フコシダーゼの異常によるオリゴ糖症)
g. 歯状核赤核淡蒼球ルイ体萎縮症
(小児に最も多い脊髄小脳変性症)
h. 尿素サイクル異常症
3. 線条体(尾状核, 被殻)病変が強い疾患
a. リー症候群
b. MELAS
(ミトコンドリア脳筋症・乳酸アシドーシス・脳卒中様発作症候群)
c. ウィルソン病
d. アレキサンダー病
(glial fibrillary acidic proteinがアストロサイトに異常蓄積)
e. エチルマロン酸血症
(ミトコンドリアのマトリックスで硫黄の分解に関わる分子の異常)
f. プロピオン酸血症 #(食事療法)
(プロピオニルCoAカルボキシラーゼ)
g. グルタル酸尿症I型 #(L-カルニチン投与, ロイシン, トリプトファン制限)
(グルタリルCoA脱水素酵素欠損症：前側頭葉形成不全をみる)
h. 3-ヒドロキシ-3-メチルグルタリル補酵素Aリアーゼ欠損症
i. モリブデン補酵素欠損症
(モリブデン補酵素の合成障害のため, 種々の酸化酵素特に亜硫酸酸化酵素活性が低下)
j. 3-メチルグルタコン酸尿症
(多くの代謝異常で起こる, 一部はロイシンの代謝異常)
k. βケトチオラーゼ欠損症
(脂肪酸からのケトン体産生に関わる酵素の欠損)

(次頁につづく)

（表1つづき）

l. マロン酸血症
（ロイシン，イソロイシン代謝最終に関わるマロニルCoAデカルボキシラーゼ欠損）
m. ビオチニダーゼ欠損症　#（ビオチン投与）
（ホロカルボキシダーゼ合成酵素欠損も含む）
n. ビオチン依存性大脳基底核症　#（ビオチン投与）
（ビオチンがチアミントランスポーターの発現を制御）
o. コケイン症候群

*新生児マススクリーニング対象疾患．

文　献

1) Northington FJ, Martin LJ: Neurodegeneration in the neonatal brain. In: Swaiman's Pediatric Neurology: Principles and Practice, 5th ed(ed by Swaiman KF), p13-28, Elsevier Saunders, 2012.
2) Barkovich AJ, Paytay Z: Metabolic, toxic, and inflammatory brain disorders. In: Pediatric Neuroimaging, 5th ed(ed by Raybaud C, Barkovich AJ), p81-239, Wolters Kluwer Health/Lippincott Williams & Wilkins, Philadelphia, 2012.
3) Gleason C, Davaskar A: Avery's Diseases of the Newborn, 9th ed, Elsevier/Saunders, Philadelphia, 2012.
4) Saudubray JM, et al(ed): Inborn Metabolic Diseases: Diagnosis and Treatment, 5th ed, Springer, Berlin, 2012.
5) チョッケ & ホフマン原著(松原洋一監訳)：小児代謝疾患マニュアル 改訂第2版(原著第3版)，診断と治療社，2013.