Ⅳ. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
山本俊至(訳)	染色体異常と大規模DNA変化を調べるための遺伝子検査技術	菅野純夫・福嶋義光	ゲノム医学	メディカルサイエンスインターナショナル	東京	2015	in press
山本俊至	ダウン症候群・染色体異常	新島新一，山内秀雄，山本仁	こどもの神経の診かた	医学書院	東京	2015	in press
山本俊至	1p36欠失症候群	水口雅，市橋光，崎山弘	今日の小児治療指針	医学書院	東京	2015	pp182-183
山本俊至	Rett症候群	水口雅，市橋光，崎山弘	今日の小児治療指針	医学書院	東京	2015	pp684-685
山本俊至(訳)	先天性疾患の疫学および遺伝的基礎	衛藤義勝	ネルソン小児科学第19版(日本語訳)	エルゼビアジャパン	東京	2015	pp1802

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Okamoto N, Toribe Y, Shimojima K, Yamamoto T.	Tatton–Brown–Rahman syndrome due to 2p23 microdeletion.	Am J Med Genet A		in press	2016
Igarashi A, Okumura A, Shimojima K, Abe S, Ikeno M, Shimizu T, Yamamoto T.	Focal seizures and epileptic spasms in a child with Down syndrome from a family with a *PRRT2* mutation.	Brain Dev		in press	

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Itakura A, Saito Y, Nishimura Y, Okazaki T, Ohno K, Sejima H, Yamamoto T, Maegaki Y.	Successful treatment of migrating partial seizures in Wolf–Hirschhorn syndrome with bromide.	Brain Dev		in press	
Sumida K, Inoue K, Takanashi J-I, Sasaki M, Watanabe K, Suzuki M, Kurahashi H, Omata T, Tanaka M, Yokochi K, Iio J, Iyoda K, Kurokawa T, Matsuo M, Sato T, Iwaki A, Osaka H, Kurosawa K, Yamamoto T, Matsumoto N, Maikusa N, Mastuda H, Sato N.	The magnetic resonance imaging spectrum of Pelizaeus–Merzbacher disease: A multicenter study of 19 patients.	Brain Dev		in press	
Yamamoto T, Igarashi N, Shimojima K, Sangu N, Sakamoto Y, Shimoji K, Niijima S.	Use of targeted next-generation sequencing for molecular diagnosis of craniosynostosis: identification of a novel de novo mutation of *EFNB1*.	Congenit Anom (Kyoto)		in press	
Yamamoto T.	Characteristics of epileptic encephalopathy related to *CDLK5* mutations.	J Pediatr Epilepsy		in press	
Oka M, Shimojima K, Yamamoto T, Hanaoka Y, Sato S, Yasuhara T, Yoshinaga H, Kobayashi K.	A novel *HYLS1* homozygous mutation in living siblings with Joubert syndrome.	Clin Genet		in press	

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Watanabe S, Shimizu K, Ohashi H, Kosaki R, Okamoto N, Shimojima K, Yamamoto T, Chinen Y, Mizuno S, Dowa Y, Shiomi N, Toda Y, Tashiro K, Shichijo K, Minatozaki K, Aso S, Minagawa K, Hiraki Y, Shimokawa O, Matsumoto T, Fukuda M, Moriuchi H, Yoshiura KI, Kondoh T.	Detailed analysis of 26 cases of 1q partial duplication/triplication syndrome.	Am J Med Genet A		in press	
Shimojima K, Okamoto N, Yamamoto T.	A novel *TUBB3* mutation in a sporadic patient with asymmetric cortical dysplasia.	Am J Med Genet A		in press	
Yamamoto T, Shimojima K, Yano T, Ueda Y, Takayama R, Ikeda H, Imai K.	Loss-of-function mutations of *STXBP1* in patients with epileptic encephalopathy.	Brain Dev	38	280-284	2016
Ishikawa N, Kobayashi Y, Fujii Y, Yamamoto T, Kobayashi M.	Late-onset epileptic spasms in a patient with 22q13.3 deletion syndrome.	Brain Dev	38	109-112	2016
Yamamoto T, Yoshioka S, Tsurusaki Y, Shino S, Shimojima K, Shigematsu Y, Takeuchi Y, Matsumoto N.	White matter abnormalities in an adult patient with L-2-hydroxyglutaric aciduria.	Brain Dev	38	142-144	2016
Sangu N, Shimojima K, Okumura A, Ando T, Yamamoto T.	Characteristics of patients with benign partial epilepsy in infancy without *PRRT2* mutations.	Epilepsy Res	118	10-13	2015
Shimojima K, Okumura A, Yamamoto T.	A de novo microdeletion involving *PAFAH1B* (*LIS1*) related to lissencephaly phenotype.	Data in Brief	118	488-491	2015

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Yamamoto T, Shimojima K, Shibata T, Akiyama M, Oka M, Akiyama T, Yoshinaga H, Kobayashi K.	Novel *PLA2G6* mutations associated with an exonic deletion due to non-allelic homologous recombination in a patient with infantile neuroaxonal dystrophy.	Human Genome Variation	2	15048	2015
Shimojima K, Okumura A, Hayashi M, Kondo T, Inoue H, Yamamoto T.	*CHCHD2* is down-regulated in neuronal cells differentiated from iPS cells derived from patients with lissencephaly.	Genomics	106	196-203	2015
Yamamoto T, Shimada S, Shimojima K, Sangu N, Ninomiya S, Kubota M.	Leukoencephalopathy associated with 11q24 deletion involving the gene encoding hepatic and glial cell adhesion molecule in two patients.	Eur J Med Genet	58	492-496	2015
Yamamoto T, Takanashi J, Kurosawa K, Deguchi K, Osaka H, Inoue K.	Comment on "Delayed myelination is not a constant feature of Allan-Herndon-Dudley syndrome: Report of a new case and review of the literature" by Azzolini S et al. Brain & Development 2014;36:716-720	Brain & Dev	37	988-989	2015
Kawahara T, Watanabe H, Omae R, Yamamoto T, Inazu T.	A novel *PHEX* mutation in Japanese patients with X-linked hypophosphatemic rickets.	Case Rep Genet 2015		301264	2015
Nishigaki S, Hamazaki T, Saito M, Yamamoto T, Seto T, Shintaku H.	Periventricular heterotopia and white matter abnormalities in a girl with mosaic ring chromosome 6.	Mol Cytogenet	8	54	2015
Yamamoto T, Shimojima K, Kimura N, Mogami Y, Usui D, Takayama R, Ikeda H, Imai K.	Recurrent occurrences of *CDKL5* mutations in patients with epileptic encephalopathy.	Human Genome Variation	2	15042	2015

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Shimojima K, Okamoto N, Yamamoto T.	Characteristics of 2p15-p16.1 microdeletion syndrome; review and description of two additional patients.	Congenit Anom (Kyoto).	55	125-132	2015
Tsurusaki Y, Tanaka R, Shimada S, Shimojima K, Nakashima M, Saitsu H, Miyake N, Yamamoto T, Matsumoto N.	Novel compound heterozygous mutations in *LIAS* cause glycine encephalopathy.	J Hum Genet	60	631-635	2015
Shimada S, Shimojima K, Sangu N, Hoshino A, Hachiya Y, Ohto T, Hashi Y, Nishida K, Mitani M, Kinjo S, Tsurusaki Y, Matsumoto N, Morimoto M, Yamamoto T.	Mutations in the genes encoding eukaryotic translation initiation factor 2B in Japanese patients with vanishing white matter disease.	Brain Dev	37	960-966	2015
Yamamoto T.	[Editorial] Epilepsy in numerical chromosomal abnormalities.	J Pediatr Epilepsy	4	2-3	2015
Yamamoto T, Shimada S, Shimojima K, Ikeda H, Oguni K.	Epilepsy in 1p36 deletion syndrome is not associated with deletion size.	J Pediatr Epilepsy	4	4-7	2015
Okumura A, Yamamoto T, Kurahashi H, Takasu M.	Epilepsies in children with 2q24.3 deletion/duplication.	J Pediatr Epilepsy	4	8-16	2015
Akiyama T, Yamamoto T.	Epilepsy and other symptoms associated with chromosome 9q34.11 microdeletion.	J Pediatr Epilepsy	4	23-29	2015
Yamamoto T, Shimada S, Shimojima K, Eto K, Yoshitomi S, Yanagihara K, Imai K, Oguni H, Okamoto N.	Xq28 duplications and epilepsy: Influence of the combinatory duplication of *MECP2* and *GDI1*.	J Pediatr Epilepsy	4	30-34	2015

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Tsurusawa R, Ihara Y, Ogawa A, Yamamoto T.	16p11.2 microdeletion/microduplication syndrome and benign infantile epilepsy.	J Pediatr Epilepsy	4	35-40	2015
Okumura A, Ishii A, Shimojima K, Kurahashi H, Yoshitomi S, Imai K, Imamura M, Seki Y, Shimizu T, Hirose S, Yamamoto T.	Phenotypes of children with 20q13.3 microdeletion affecting *KCNQ2* and *CHRNA4*.	Epileptic Disord	17	165-171	2015
Yamamoto T, Shimojima K.	A novel *MED12* mutation associated with non-specific X-linked intellectual disability.	Human Genome Variation	2	15018	2015
Mimaki M, Shiihara T, Watanabe M, Hirakata K, Sakazume S, Ishiguro A, Shimojima K, Yamamoto T, Oka A, Mizuguchi M.	Holoprosencephaly with cerebellar vermis hypoplasia in 13q deletion syndrome: Critical region for cerebellar dysgenesis within 13q32.2q34.	Brain Dev	37	714-718	2015
Yoshitomi S, Takahashi Y, Ishizuka M, Yamaguchi T, Watanabe A, Nasu H, Ueda Y, Ohtani H, Ikeda H, Imai K, Shigematsu H, Inoue Y, Tanahashi Y, Aiba K, Ohta H, Shimada S, Yamamoto T.	Three patients manifesting early infantile epileptic spasms associated with 2q24.3 microduplications.	Brain Dev	37	874-879	2015
Okumura A, Arai E, Kitamura Y, Abe S, Ikeno M, Fujimaki T, Yamamoto T, Shimizu T.	Epilepsy phenotypes in siblings with Norrie disease.	Brain Dev	37	978-982	2015

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Aoyama Y, Yamamoto T, Sakaguchi N, Ishige M, Tanaka T, Ichihara T, Ohara K, Kouzan H, Kinosada Y, Fukao T.	Application of multiplex ligation-dependent probe amplification, and identification of a heterozygous Alu-associated deletion and a uniparental disomy of chromosome 1 in two patients with 3-hydroxy-3-methylglutaryl-CoA lyase deficiency.	Int J Mol Med	35	1554-1560	2015
Masuda T, Ueda M, Ueyama H, Shimada S, Ishizaki M, Imamura S, Yamamoto T, Ando Y.	Megalencephalic leukoencephalopathy with subcortical cysts caused by compound heterozygous mutations in *MLC1*, in patients with and without subcortical cysts in the brain.	J Neurol Sci	351	211-213	2015
Shimojima K, Okumura A, Ikeno M, Nishimura A, Saitoh A, Saitsu H, Matsumoto N, Yamamoto T.	A de novo *TUBB4A* mutation in a patient with hypomyelination mimicking Pelizaeus-Merzbacher disease.	Brai Dev	37	281-285	2015
Shimada S, Shimojima K, Okamoto N, Sangu N, Hirasawa K, Matsuo M, Ikeuchi M, Shimakawa S, Shimizu K, Mizuno S, Kubota M, Adachi M, Saito Y, Tomiwa K, Haginoya K, Numabe H, Kako Y, Hayashi A, Sakamoto H, Hiraki Y, Minami K, Takemoto K, Watanabe K, Miura K, Chiyonobu T, Kumada T, Imai K, Maegaki Y, Nagata S, Kosaki K, Izumi T, Nagai T, Yamamoto T.	Microarray analysis of 50 patients reveals the critical chromosomal regions responsible for 1p36 deletion syndrome-related complications.	Brai Dev	37	515-526	2015

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Yamamoto T, Shimojima K, Sangu N, Komoike Y, Ishii A, Abe S, Yamashita S, Imai K, Kubota T, Fukasawa T, Okanishi T, Enoki H, Tanabe T, Saito A, Furukawa T, Shimizu T, Milligan CJ, Petrou S, Heron SE, Dibbens LM, Hirose S, Okumura A.	Single nucleotide variations in *CLCN6* identified in patients with benign partial epilepsies in infancy and/or febrile seizures.	Plos One	10	e0118946	2015
Shimojima K, Okamoto N, Tamasaki A, Sangu N, Shimada S, Yamamoto T.	An association of 19p13.2 microdeletions with Malan syndrome and Chiari malformation.	Am J Med Genet A	167A	724-730	2015
Chong PF, Haraguchi K, Torio M, Kirino M, Ogata R, Matsukura M, Sakai Y, Ishizaki Y, Yamamoto T, Kira R.	A case of pontine tegmental cap dysplasia with comorbidity of oculoauriculovertebral spectrum.	Brain Dev	37	171-174	2015
Furukawa T, Sakamoto H, Takeuchi S, Ameri M, Kuboki Y, Yamamoto T, Hatori T, Yamamoto M, Sugiyama M, Ohike N, Yamaguchi H, Shimizu M, Shibata N, Shimizu K, Shiratori K.	Whole exome sequencing reveals recurrent mutations in *BRCA2* and *FAT* genes in acinar cell carcinomas of the pancreas.	Sci Rep	5	8829	2015
Okami N1, Aihara Y, Akagawa H, Yamaguchi K, Kawashima A, Yamamoto T, Okada Y.	Network-based gene expression analysis of vascular wall of juvenile Moyamoya disease.	Childs Nerv Syst	31	399-404	2015
山本俊至	遺伝カウンセリング	特集 周産期医学必修知識 第8版「周産期医学」	46巻増刊号	in press	2015

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
山本俊至	マイクロアレイ染色体検査	検査と技術		in press	2015
山本俊至	マイクロアレイ染色体検査	小児内科	47	1809-1812	2015
島田姿野，山本俊至	感染症をきっかけに退行が進行する1歳男児	日本小児神経学会 編 続・イメージからせまる小児神経疾患 診断と治療社		pp47-48	2015
山本俊至	マイクロアレイ染色体検査	『小児内科』『小児外科』編集委員会 共編 小児疾患診療のための病態生理2小児内科	47巻増刊号	pp184-190	
山本俊至	染色体検査とアレイCGH	松原洋一，呉繁夫，左合治彦［編］こどもの病気 遺伝について聞かれたら 診断と治療社		pp237-240	2015
山本俊至	アレイCGH法によるてんかんの分子診断.	医学のあゆみ	253	543-547	2015

Ⅴ．研究成果の刊行の刊行物・別刷

ELSEVIER

Brain & Development 38 (2016) 142–144

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

www.elsevier.com/locate/braindev

Case Report

White matter abnormalities in an adult patient with L-2-hydroxyglutaric aciduria

Toshiyuki Yamamoto [a,*], Seiichiro Yoshioka [b], Yoshinori Tsurusaki [c], Shimada Shino [a,d], Keiko Shimojima [a], Yosuke Shigematsu [e], Yoshihiro Takeuchi [b], Naomichi Matsumoto [c]

[a] *Tokyo Women's Medical University Institute for Integrated Medical Sciences, Tokyo, Japan*
[b] *Department of Pediatrics, Shiga Medical University, Ohtsu, Japan*
[c] *Department of Human Genetics, Yokohama City University Graduate School of Medicine, Yokohama, Japan*
[d] *Department of Pediatrics, Tokyo Women's Medical University, Tokyo, Japan*
[e] *Department of Health Science, Faculty of Medical Sciences, University of Fukui, Japan*

Received 7 April 2015; received in revised form 30 April 2015; accepted 30 April 2015

Abstract

L-2-Hydroxyglutaric aciduria (L-2-HGA) is a rare inborn error of metabolism. Mainly, patients with this disorder exhibit neurological symptoms and characteristic neuroradiological findings, such as subcortical white matter abnormalities, which are believed to be caused by the toxicity of the accumulation of L-2-hydroxyglutaric acid. A genotype-first approach of the whole exome sequence was used to identify compound heterozygous mutations, c.584A>G (p.Y195C) and c.772T>C (p.C258R), in *L2HGDH*, the gene responsible for this disorder, in an adult patient with intellectual disability and intractable epilepsy. A retrospective assay confirmed the increased concentrations of 2-hydroxyglutaric acid in the urine. These results suggested that neuroradiological findings of subcortical white matter abnormalities are characteristic of L-2-HGA and that clinical exome sequencing has sufficient power to compensate for insufficient clinical evaluations.

Keywords: L-2-Hydroxyglutaric aciduria (L-2-HGA); *L2HGDH*; Subcortical white matter abnormalities; Genotype-first approach; Clinical exome sequencing

1. Introduction

L-2-Hydroxyglutaric aciduria (L-2-HGA; MIM#236792) is a rare inborn error of metabolism, which involves defects in the metabolism of L-2-hydroxyglutaric acid, which results in increased levels of the acid in the urine. Since the first case was described in 1980 [1], some cases have been reported in Japan [2] and worldwide. The gene responsible for this disorder, *L2HGDH*, which is located on chromosome 14q22.1, was identified in 2004 [1]. The pathogenesis of the accumulation of L-2-hydroxyglutaric acid is unclear, but it is probably toxic to the white matter through myelin vacuolation [3]. Consequently, the neuroradiological findings in these patients are unique, and the subcortical white matter abnormalities can be visualized with brain magnetic resonance imaging (MRI) [4].

Although the diagnosis of an inborn error of metabolism can generally be made by screening of the metabolic

* Corresponding author at: Tokyo Women's Medical University Institute for Integrated Medical Sciences, 8-1 Kawada-cho, Shinjuku-ward, Tokyo 162-8666, Japan. Tel.: +81 3 3353 8112x24013; fax: +81 3 5269 7667.
E-mail address: yamamoto.toshiyuki@twmu.ac.jp (T. Yamamoto).

http://dx.doi.org/10.1016/j.braindev.2015.04.012
0387-7604/

substrate, such an error is often undiagnosed because of phenotypic heterogeneity. Recent advancements in molecular analysis equipment have overcome this dilemma in clinical diagnosis. Some cases with inborn error of metabolism have been diagnosed with genotype-first approach and not by metabolism screening [5,6]. Here, we present a new patient with L-2-HGA who exhibited white matter abnormalities and who was diagnosed by clinical exome sequencing.

2. Patient report

A 33-year-old female patient was born with a birth weight of 2500 g (mean), a length of 47.5 cm (25th–50th centile), and an occipitofrontal circumference (OFC) of 32 cm (10th–20th centile). Her parents were non-consanguineous and healthy. She has four siblings. She started to show recurrent febrile seizures at 7 months. She began to walk with supports at 10 months and to talk with meaningful words at 9 months. Her neurodevelopment was within normal limits until 8 years of age. At that time, she exhibited nonfebrile seizures. Because an electroencephalography showed right-frontal dominant spike and wave discharges, anti-epileptic drugs were prescribed. Subsequently, her psychomotor development gradually delayed. Her generalized tonic seizures were intractable, and several attacks were observed per year. Because her intellectual capacity is at the approximate level of a 5-year-old, she lives in a group home that is supported by welfare.

At 33 years of age, she suddenly showed status epilepticus that was associated with drowsiness and without any trigger. She was immediately transferred to the hospital. Although she recovered consciousness after treatment, a brain MRI revealed abnormal findings in the white matter for the first time (Fig. 1).

At present, her height is 164 cm (90th–97th centile), her weight is 85 kg (>97th centile), and her OFC is 54 cm (10th centile), which indicates that she is obese with a body mass index of 31.6. A physical examination showed no abnormalities. A neurological examination revealed mild ataxia and dystonic posture. After obtaining the molecular diagnosis, combined D-2- and L-2-hydroxyglutaric acid levels in urine were measured using urease-pretreatment of urine, trimethylsilylation, and gas chromatography-mass spectrometry [7]. Although an increased concentration was detected, D-2- and L-2-hydroxyglutaric acids cannot be separated in this method.

3. Molecular analysis

The ethical committee of Tokyo Women's Medical University approved this study. After obtaining written informed consent from the patient's family, blood samples were obtained from the patient and her parents. DNA was extracted from the blood samples using QIAamp DNA extraction kit (QIAGEN GmbH, Hilden, Germany). DNA from the patient and her parents were analyzed with whole exome sequencing as previously described [8].

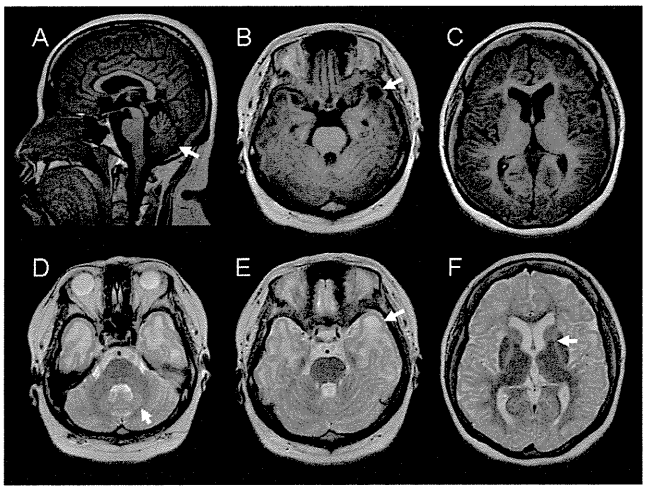

Fig. 1. The results of the brain magnetic resonance imaging that was performed on the patient at 33 years of age. (A) A T1-weighted sagittal image shows remarkable folia of the cerebrum (arrow), indicating mild atrophy. (B and C) T1-weighted axial images. (D–F) T2-weighted axial images. Diffuse subcortical white matter abnormalities are noted in axial images. Some of the subcortical regions (arrows) show cystic changes (B and D). The involvement of the dentate nucleus (arrow) is characteristic (D). Signal high intensity is shown in the anterior and posterior limbs of internal capsule (F). Dilatations of the lateral ventricles and extra-cerebral spaces indicate diffuse brain atrophy.

We focused on *de novo* and recessive mutations. Although there were no *de novo* mutations that have functional relevance to neurological disorders, we identified the following compound heterozygous mutations of *L2HGDH*: c.584A>G (p.Y195C) and c.772T>C (p.C258R). These mutations were transmitted from her father and mother, respectively. Sanger sequencing confirmed these findings (Fig. 2). The c.772T>C mutation is registered in the dbSNP137 SNP database as rs145390085, and it has a frequency of 0.007% in the National Heart, Lung, and Blood Institute Exome Sequencing Project (NHLBI-ESP) 6500 (http://evs.gs.washington.edu/EVS/). The c.584A>G mutation is not registered in the dsSNP137 SNP database, NHLBI-ESP 6500, Human Genetic Variation Browser database (http://www.genome.med.kyoto-u.ac.jp/SnpDB/), or in any of our 575 in-house Japanese control exome databases. The c.584A>G and c.772T>C mutations were predicted to be damaging by SIFT (http://sift.jcvi.org/) scores of 0.00 for both, Polyphen-2 (http://genetics.bwh.harvard.edu/pph2/) scores of 0.986 and 1.000, respectively, and MutationTaster (http://neurocore.charite.de/MutationTaster/) scores of 1.000 for both.

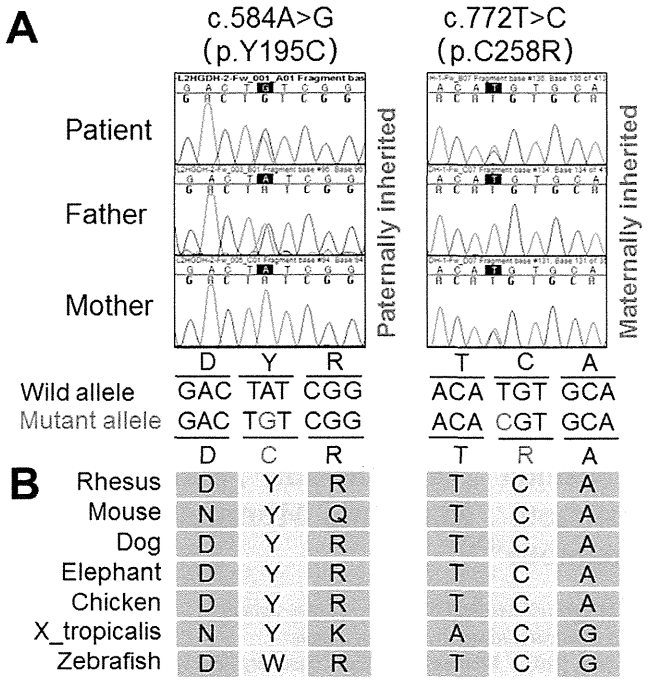

Fig. 2. The results of the molecular analysis. (A) Sanger sequencing confirms compound heterozygous mutations that are transmitted from both parents. (B) The affected amino acids are conserved among mammals.

4. Discussion

In this study, we identified compound heterozygous variants of *L2HGDH* in an adult patient with epilepsy and intellectual disability. The paternally transmitted c.584A>G mutation was previously reported as a disease-causing mutation by Sass et al. [9]. In comparison, the maternally transmitted c.772T>C mutation was registered in the dbSNP database. However, its frequency was extremely low (0.007%), and the prediction software suggested that the consequence of this variant would be damaging. Therefore, we concluded that this variant was pathogenic. Urine screening that was performed after identification of the *L2HGDH* mutations detected an increased concentration of 2-hydroxyglutaric acid in the urine, and a final diagnosis of L-2-HGA was made in this patient.

Although this patient did not show developmental delay in early infancy, she started to show epilepsy and subsequent developmental deterioration at 8 years of age. This clinical course is typical for patients with L-2-HGA [10], but it is not specific and is also rather frequently observed in the histories of patients with intractable epilepsy. From the characteristic white matter abnormalities that were revealed by MRI, which the patient first underwent at 33 years of age after her status epilepticus, we suspected leukoencephalopathy, and we performed genetic screening. Although a diagnosis of L-2-HGA is generally made after findings of highly increased levels of L-2-hydroxyglutaric acid in the urine, a urine screening was never performed in this patient before the exome sequencing results were obtained. Therefore, a brain MRI examination and urine screening should have been performed in the early stages of the disease in this patient. Furthermore, a candidate diagnosis of L-2-HGA might have possibly been obtained after careful evaluation of the characteristic MRI findings [4]. Because there is a report of therapeutic approach using riboflavin, early diagnosis of L-2-HGA would be required [1].

Acknowledgements

We would like to express our gratitude to the patient and her parents for their cooperation. This work was supported by a Grant-in-Aid for Scientific Research from Health Labor Sciences Research Grants from the Ministry of Health, Labor, and Welfare, Japan.

References

[1] Kranendijk M, Struys EA, Salomons GS, Van der Knaap MS, Jakobs C. Progress in understanding 2-hydroxyglutaric acidurias. J Inherit Metab Dis 2012;35:571–87.
[2] Fujitake J, Ishikawa Y, Fujii H, Nishimura K, Hayakawa K, Inoue F, et al. L-2-Hydroxyglutaric aciduria: two Japanese adult cases in one family. J Neurol 1999;246:378–82.
[3] van der Knaap MS, Jakobs C, Hoffmann GF, Nyhan WL, Renier WO, Smeitink JA, et al. D-2-Hydroxyglutaric aciduria: biochemical marker or clinical disease entity? Ann Neurol 1999;45:111–9.
[4] Steenweg ME, Salomons GS, Yapici Z, Uziel G, Scalais E, Zafeiriou DI, et al. L-2-Hydroxyglutaric aciduria: pattern of MR imaging abnormalities in 56 patients. Radiology 2009;251:856–65.
[5] Prada CE, Gonzaga-Jauregui C, Tannenbaum R, Penney S, Lupski JR, Hopkin RJ, et al. Clinical utility of whole-exome sequencing in rare diseases: galactosialidosis. Eur J Med Genet 2014;57:339–44.
[6] Schuster J, Khan TN, Tariq M, Shaiq PA, Mabert K, Baig SM, et al. Exome sequencing circumvents missing clinical data and identifies a BSCL2 mutation in congenital lipodystrophy. BMC Med Genet 2014;15:71.
[7] Kuhara T. Diagnosis and monitoring of inborn errors of metabolism using urease-pretreatment of urine, isotope dilution, and gas chromatography-mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci 2002;781:497–517.
[8] Tsurusaki Y, Koshimizu E, Ohashi H, Phadke S, Kou I, Shiina M, et al. De novo SOX11 mutations cause Coffin–Siris syndrome. Nat Commun 2014;5:4011.
[9] Sass JO, Jobard F, Topcu M, Mahfoud A, Werle E, Cure S, et al. L-2-Hydroxyglutaric aciduria: identification of ten novel mutations in the L2HGDH gene. J Inherit Metab Dis 2008;31(Suppl.):S275–9.
[10] Steenweg ME, Jakobs C, Errami A, van Dooren SJ, Adeva Bartolome MT, Aerssens P, et al. An overview of L-2-hydroxyglutarate dehydrogenase gene (L2HGDH) variants: a genotype-phenotype study. Hum Mutat 2010;31:380–90.

ELSEVIER

Brain & Development 37 (2015) 960–966

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

www.elsevier.com/locate/braindev

Original article

Mutations in the genes encoding eukaryotic translation initiation factor 2B in Japanese patients with vanishing white matter disease

Shino Shimada [a,b], Keiko Shimojima [a], Noriko Sangu [a,c], Ai Hoshino [d], Yasuo Hachiya [d], Tatsuyuki Ohto [e], Yuichiro Hashi [f], Katsuya Nishida [g], Maki Mitani [g], Saori Kinjo [h], Yoshinori Tsurusaki [i], Naomichi Matsumoto [i], Masafumi Morimoto [j], Toshiyuki Yamamoto [a,*]

[a] *Tokyo Women's Medical University Institute for Integrated Medical Sciences, Tokyo, Japan*
[b] *Department of Pediatrics, Tokyo Women's Medical University, Tokyo, Japan*
[c] *Department of Oral and Maxillofacial Surgery, School of Medicine, Tokyo Women's Medical University, Tokyo, Japan*
[d] *Department of Neuropediatrics, Tokyo Metropolitan Neurological Hospital, Fuchu, Japan*
[e] *Department of Pediatrics, Tsukuba University, Tsukuba, Japan*
[f] *Department of Neurology, National Hospital Organization Kyoto Medical Center, Kyoto, Japan*
[g] *Department of Neurology, National Hospital Organization Hyogo-Chuo National Hospital, Sanda, Japan*
[h] *Department of Pediatrics, Okinawa Chubu Hospital, Uruma, Japan*
[i] *Department of Human Genetics, Yokohama City University Graduate School of Medicine, Yokohama, Japan*
[j] *Department of Pediatrics, Kyoto Prefectural University of Medicine, Kyoto, Japan*

Received 29 September 2014; received in revised form 4 March 2015; accepted 19 March 2015

Abstract

Objective: Vanishing white matter disease (VWM) is a chronic, progressive leukoencephalopathy associated with episodes of rapid deterioration following minor stress events such as head traumas or infectious disorders. The white matter of the patients with VWM exhibits characteristic radiological findings.

Method: The genes encoding all five subunits of eukaryotic translation initiation factor 2B (EIF2B) were analyzed in patients, who were tentatively diagnosed with VWM, by Sanger sequencing.

Results: Seven mutations were identified in the genes encoding the subunits 1, 2, 4, and 5 of EIF2B. Among them, one mutation (p.V83E) in the subunit 2 (*EIF2B2*) was recurrently identified in three alleles, indicating the most common mutation in Japanese patients with VWM. Two patients were homozygous, and the other four patients were compound heterozygous.

Conclusion: All patients showed white matter abnormalities with various degrees. One patient showed manifestations of end-stage VWM disease. Some patients showed late onset and slow progression associated with brain magnetic resonance imaging displaying T2 high intensity only in the deep white matter. There was clinical heterogeneity among patients with VWM.

Keywords: Vanishing white matter disease (VWM); Eukaryotic translation initiation factor 2B (EIF2B); Leukoencephalopathy; Mutation

* Corresponding author at: Tokyo Women's Medical University Institute for Integrated Medical Sciences, 8-1 Kawada-cho, Shinjuku-ward, Tokyo 162-8666, Japan. Tel.: +81 3 3353 8112x24013; fax: +81 3 5269 7667.
E-mail address: yamamoto.toshiyuki@twmu.ac.jp (T. Yamamoto).

http://dx.doi.org/10.1016/j.braindev.2015.03.003
0387-7604/

1. Introduction

Childhood ataxia with central hypomyelination (CACH) or leukoencephalopathy with vanishing white matter (VWM; MIM #603896) is a chronic, progressive leukoencephalopathy associated with episodes of rapid deterioration following minor stress events such as head trauma or infectious disorders [1–3]. Patients with VWM show abnormal radiological findings in the brain; i.e., the cerebral white matter appears progressively diffuse and symmetrical abnormalities such as rarefaction and cysts. VWM is an autosomal recessive disease caused by mutations in any of the genes encoding the subunits of eukaryotic translation initiation factor 2B (EIF2B), which is a GTP exchange protein essential for protein synthesis [4,5]. Until now, many disease-causing mutations have been identified [6–16].

In this study, we report on the results of our on-going study to obtain genetic diagnosis for Japanese patients with VWM.

2. Materials and methods

2.1. Patients and samples

This study was approved by the ethics committee at the Tokyo Women's Medical University. After obtaining written informed consents from patients or their families, blood samples were obtained from patients. Patients were recruited under candidate diagnosis of VWM as defined by previously proposed diagnostic criteria by van der Knaap et al. [17]. In the early stages of VWM, white matter involvements may not fulfill the criteria. Therefore, patients who did not show full manifestations but were tentatively diagnosed as VWM were also included in this study. Genomic DNAs were extracted from blood samples using the QIAamp DNA Mini Kit (QIAGEN, Hamburg, Germany). Parental samples were also obtained to confirm inheritance patterns.

2.2. Molecular analysis

All exons of the genes encoding the five subunits of EIF2B (*EIF2B1*, *EIF2B2*, *EIF2B3*, *EIF2B4*, and *EIF2B5*) were genotyped using standard Sanger sequencing. Information on the primers used for this study can be obtained upon request. When heterozygous or homozygous variations were identified in patients, inherited patterns were analyzed using corresponding parental samples. PCR products were subcloned into the pGEM® T-vector (Promega, Madison, WI) to identify the allelic locations of the mutation as described previously [18]. Subsequently, nucleotide sequences of inserted fragments were analyzed in both directions. When a *de novo* mutation was suspected, the biological relationship between the patient and the corresponding parental samples was confirmed by microsatellite marker analysis using the Linkage Mapping Set (Life Technologies, Foster City, CA) as described previously [19].

The identified non-synonymous variants were tested for mutational effects using damaging predication scores obtained from the SIFT [20] (http://sift.jcvi.org/), PolyPhen-2 [21] (http://genetics.bwh.harvard.edu/pph2/), and Combined Annotation-Dependent Depletion (CADD) [22] (http://cadd.gs.washington.edu/info) in accordance with methods reported elsewhere [23]. Interspecies amino acids conservation was checked using the UCSC Genome Bioinformatics Site (https://genome.ucsc.edu/).

3. Results

3.1. Pathogenic mutations

We analyzed a total of 22 patients. Among them, we identified mutations in the genes encoding the EIF2B subunits in six patients including four unrelated individuals and two siblings. All identified mutations were missense mutations (Supplemental Figs. 1 and 2). The results of the molecular analyses in accordance with the clinical information of the patients are summarized in Table 1. Patients 1 and 2 showed homozygous mutations in *EIF2B1* and *EIF2B2*, respectively. Patient 2 was homozygous for p.V83E in *EIF2B2*, and patient 3 had compound heterozygous mutations associated with p.V83E in *EIF2B2*. The other patients showed compound heterozygous mutations in either of *EIF2B2*, *EIF2B4* and *EIF2B5*. Parental origins of all mutations other than p.M305I were confirmed (Table 1). Predicted scores for the deleterious effects of mutations provided by SIFT, Polyphen-2, and CADD are included in Table 1.

Both p.M305I and p.I385T were identified in exon 7 of *EIF2B5* in patient 6. To assess the allelic locations of these two mutations, PCR products were subcloned into the plasmid vector. At least 10 clones were isolated and sequenced. Consequently, all clones showed one of the mutations, indicating that the two mutations were located on the independent alleles. Although p.I385T was identified in the patient's mother, p.M305I was not identified in both parents. We confirmed the biological relationship between patient 6 and his parents by linkage analysis (data not shown).

3.2. Patient reports

Patient 1 is a 61-year-old female, whose parents were cousins. Initial neurological symptoms with gait disturbance were first observed at 29 years of age. At that time, her intellectual quotient was evaluated to be 66. Motor incoordination and spasticity were also noted. Routine laboratory examinations of blood, urine, and

Table 1
Summaries of the clinical information of the patients and the results of mutation analyses.

Patients	Patient 1	Patient 2	Patient 3		Patient 4		Patient 5		Patient 6	
Clinical information										
Gender	F	F	M		M		M		M	
Present age (y/m)	61y	8y	8 m		22y		19y		5y5m	
Onset age (y/m)	29y	3y	8 m		13y		13y		13m	
Provoking event	–	Infection	Infection (fever)		Lack of sleep		Head trauma		Infection (fever)	
Seizure	+	+	+		+		–		+	
Disturbed consciousness	+	+	+		–		+		+	
Other neurological findings	Bedridden	Bulbar paralysis	Spasticity, developmental delay		Mild ataxia		Muscular weakness		Gait disturbance	
Consanguinity	+	–	–		–		–		–	
Family history	–	–	–		The elder brother of Pt. 5		The younger brother of Pt. 4		–	
Identified mutations										
Genes	*EIF2B1*	*EIF2B2*	*EIF2B2*		*EIF2B4*		*EIF2B4*		*EIF2B5*	
Chromosomal location	12q24.31	14q24.3	14q24.3		2p23.3		2p23.3		3q27.1	
Inheritance	Homozygous	Homozygous	Compound heterozygous		Compound heterozygous		Compound heterozygous		Compound heterozygous	
Exon	exon 8	exon 2	exon 2	exon 5	exon 6	exon 11	exon 6	exon 11	exon 7	exon 7
Nucleotide alteration	c.715T>G	c.254T>A	c.254T>A	c.682A>G	c.556T>A	c.1070G>A	c.556T>A	c.1070G>A	c.915G>A	c.1154T>C
Amino-acid change	p.F239V	p.V85E	p.V85E	p.R228G	p.Y186N	p.R357Q	p.Y186N	p.R357Q	p.M305I	p.I385T
Novel/ recurrent	Novel	Recurrent	Recurrent	Novel	Novel	Recurrent	Novel	Recurrent	Novel	Novel
Origin	Not confirmed	Both parents	Paternal	Maternal	Maternal	Paternal	Maternal	Paternal	*de novo*	Maternal
dbSNP build 138	–	–	–	–	–	rs113994033	–	rs113994033	–	–
Damaging prediction										
SIFT score	0.12	0.00	0.00	0.00	0.25	0.15	0.25	0.15	0.13	0.00
SIFT prediction	T	D	D	D	T	T	T	T	T	D
Polyphen2 HVAR score	0.715	0.995	0.995	0.999	0.979	0.637	0.979	0.637	0.196	0.95
Polyphen2 HVAR prediction	P	D	D	D	D	P	D	P	B	D
CADD score (raw)	5.436	5.264	5.264	3.760	4.290	5.227	4.290	5.227	3.735	4.732
CADD score (PHRED-like)	35.0	33.0	33.0	19.1	22.4	33.0	22.4	33.0	19.0	26.4

F, female; M, male; y, years; m, months; Pt., Patient; HVAR, HumVar-trained model autosomal recessive pattern; T, tolerate; D, damaging; B, benign.

cerebrospinal fluid (CSF) showed normal results. Enzyme activities including arylsulfatase A, β-hexosaminidase A, β-mannosidase, and α-fucosidase were within the normal limits. The motor nerve conduction velocity of the left peroneal nerve was 32 m/s, which indicated a delay. Cranial computed tomography showed diffusely distributed low-absorption in the white matter (no more detailed information). Her neurological deterioration progressed, and she is now bedridden. Brain magnetic resonance imaging (MRI) performed at 60 years of age showed diffuse high intensity in the T2-weighted images (Fig. 1).

Patient 2 is an 8-year-old girl. Language developmental delay was noted at 3 years of age. At 7 years, she was admitted to the hospital due to drowsiness after an infectious disease of mycoplasma pneumonia. Due to frequent seizures and respiratory failure, intubation was performed. Brain MRI showed diffuse T2 high

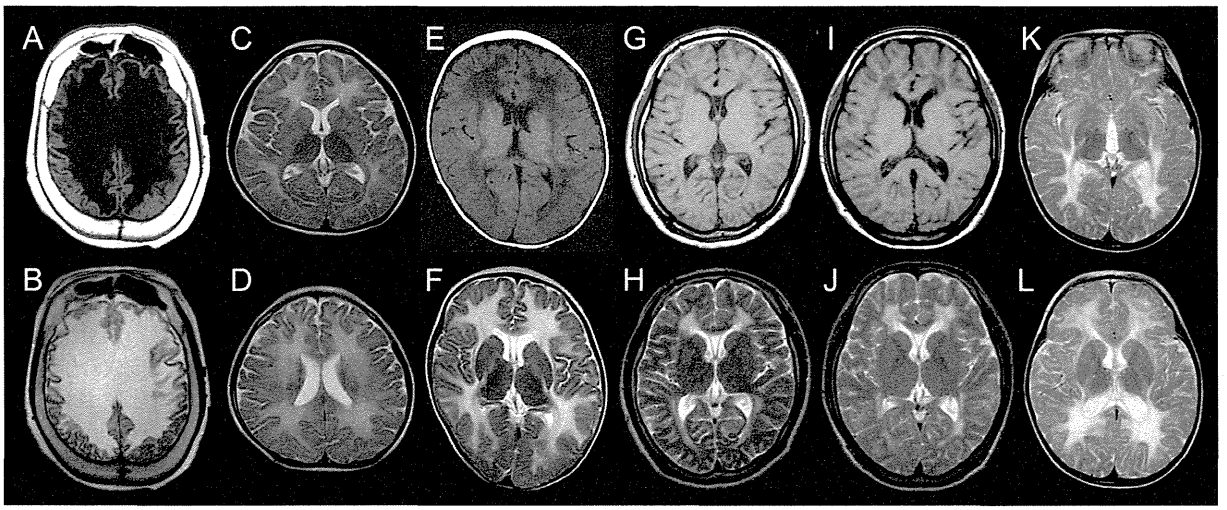

Fig. 1. Brain MRI findings of the patients examined. Axial images show various degrees of abnormal white matter. (A and B) Patient 1 examined at 60 years of age. (C and D) Patient 2 examined at 3 years of age. (E and F) Patient 3 examined at 8 months of age. (G and H) Patient 4 examined at 13 years of age. (I and J) Patient 5 examined at 16 years of age. (K and L) Patient 6 examined at 13 months of age. T1-weighted axial images (A, E, G, and I) and T2-weigthed axial images (B–D, F, H, and J–L). Periventricular zones of patient 1 are not distinguished (A and B). T2-high intensity is only shown in deep white matter, indicating early disease stage in patient 4 and 5 (H and J, respectively).

intensity in the white matter (Fig. 1). Routine laboratory examinations of blood, urine, and CSF showed no abnormality. Her neurological findings have gradually improved. At present, she can speak simple sentences and can walk unassisted.

Patient 3, a baby boy, was born with a weight of 2878 g (25th–50th centile), a length of 49.4 cm (50th–75th centile), and occipitofrontal circumference (OFC) of 33.0 cm (25th–50th centile) at 41 weeks of gestation. At 6 months of age, he showed postnatal growth delay with a weight of 6.2 kg (<3rd centile), a length of 63.4 cm (3rd–10th centile), and OFC of 42 cm (10th–25th centile). Although he showed normal development until 8 months of age, he suddenly displayed drowsiness and poor sucking after an infectious disorder causing high fever, and was admitted to the hospital. At that time, the brain MRI showed diffuse T2 high intensity in the white matter (Fig. 1). Routine laboratory examinations of blood, urine, and CSF, including lactate and pyruvate, showed no abnormality. Screening tests for metabolic disorders of amino acids and very long chain fatty acids also appeared normal. Thereafter, he showed spasticity and severe developmental delay.

Patient 4 is a 22-year-old male, first born from non-consanguineous parents. At the age of 13 years, he started to show epileptic seizures. At that time, brain MRI showed diffuse T2 high intensity in the white matter. Screening tests for metabolic disorders of amino acids and very long chain fatty acids showed normal patterns in patient 4. Enzyme activity of arylsulfatase A and β-galactosidase as well as peripheral nerve conduction velocities, were all within the normal limit. At present, he only shows mild ataxia. Patient 5, the 19-year-old younger brother of patient 4, is the third born among three siblings; his elder sister (the second born) is healthy. Patient 5 also showed a clinical course similar to that of patient 4; he showed epileptic seizures and brain MRI abnormality at age 13 years. When he was 16 years old, a traumatic accident triggered disease progression; he showed prolonged delirium, and then muscular weakness in his left side. Routine laboratory examinations of blood, urine, and CSF showed no abnormality in this sibling case.

Patient 6 is a 3-year and 5-month-old boy. There was no remarkable family or past history. At 13 months, he showed transient drowsiness and gait disturbance two weeks after a febrile convulsion. Brain MRI showed T2 high intensity in the white matter (Fig. 1). After 2 years of age, he easily dropped due to ataxic gait. At present, his height is 95.1 cm (25th–50th centile), weight is 15.9 kg (75th–90th centile), and OFC is 51.8 cm (90th–97th centile). He cannot stand alone due to spasticity in his lower extremities. Compared to motor development, his cognitive development was within the normal limit. Screening tests for metabolic disorders of amino acids and very long chain fatty acids showed normal patterns. Enzyme activities including arylsulfatase A, β-hexosaminidase A, β-galactosidase, galactosylceramidase were within the normal limits. There were no mutations in the glial fibrillary acidic protein gene (*GFAP*) nor the megalencephalic leukoencephalopathy with subcortical cysts 1 gene (*MLC1*).

4. Discussion

In this study, a molecular diagnosis of VWM was established in six patients from five families (Table 1). All of the identified mutations are depicted in the

primary structures of EIF2B genes together with previously reported mutations (Fig. 2) [4–16]. The damage prediction scores of the identified mutations were calculated and summarized in Table 1. Although the some of the predictions from SIFT and Polyphen-2 appeared benign or tolerated, all CADD scores (PHRED-like) were higher than 15. Thus, mutations identified in this study likely to have pathogenic effects.

In patient 6, p.I385T was inherited from his mother; however, p.M305I was not identified either parent. Therefore, p.M305I was suspected to be of *de novo* origin in the paternally derived allele. The UCSC Genome Bioinformatics Site displays the different single nucleotide polymorphisms (SNPs) in the same residues, p.M305L (rs200143780) and p.I385V (rs113994073) (Supplemental Fig. 2). The p.I385V is registered as a "flagged" SNP and has previously been reported as pathogenic [24] (Fig. 2). Compared to this, p.M305L is not shown as a "flagged" in the database; however, the minor allele frequency (MAF) of p.M305L is reported to be as low as 0.050% (1/2000). Because VWM is caused by an autosomal recessive trait, existence of only one individual with heterozygosity of p.M305L among 1000 normal populations may suggest that this individual is a healthy carrier of this possibly disease-causing variant. Therefore, existence of the different SNP of this residue (p.M305L) in the database does not deny pathogenesis of p.M305I. These findings indicate that these two variants are likely deleterious.

Among the 10 alleles present in the five families, three alleles (30%) shared the p.V85E mutation in *EIF2B2*. Previously, p.V85E has been identified in Japanese

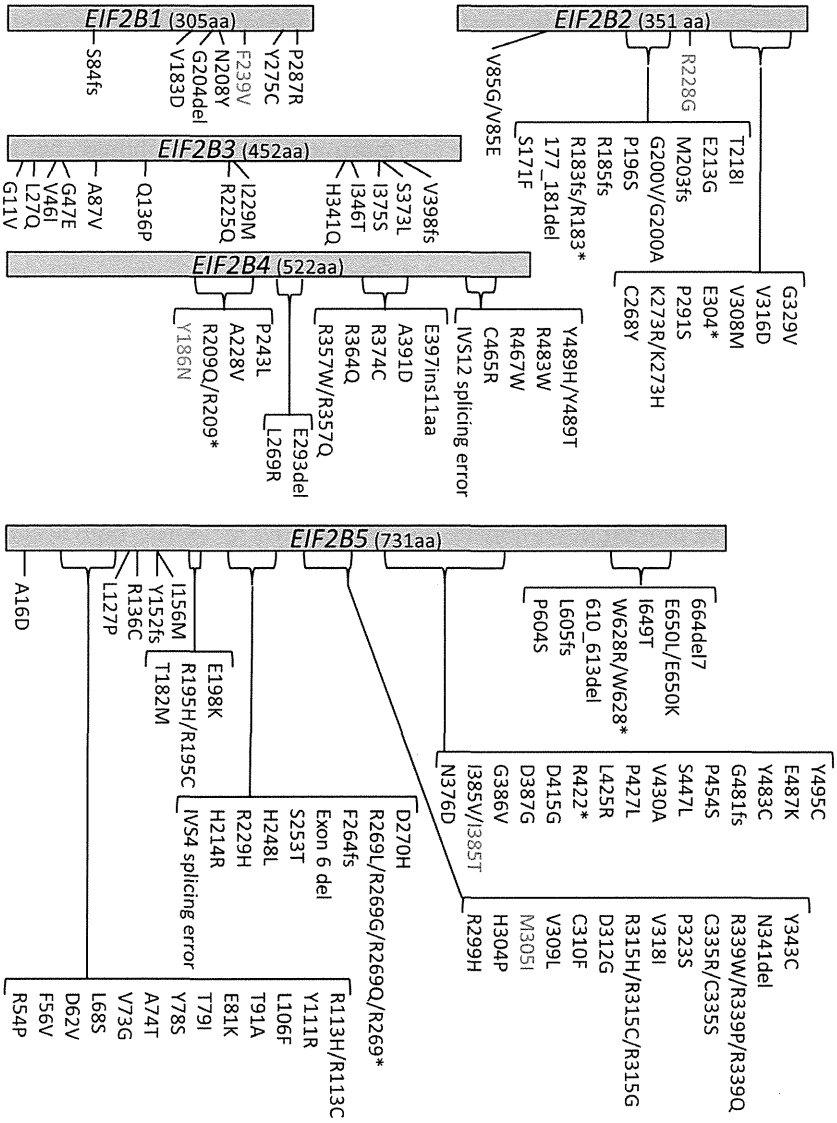

Fig. 2. Schematic representation of the distribution of EIF2B gene mutations. The novel mutations identified in this study are depicted on the primary structures of EIF2B genes in red characters, while known mutations are shown in black. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

patients [25]. We also reported this mutation in a patient with VWM, which was unmasked by a microdeletion of the homologous allele [26]. Therefore, this mutation is most common in the Japanese population. Because p.V85E has also identified in a Chinese patient [13], this variant may be common in individuals of east Asian origin. Other than p.V85E in *EIF2B2*, p.R357Q in *EIF2B4*, registered as rs113994033, was recurrently identified in the literature [8]. The other five mutations identified in this study were novel and have not been reported previously (Table 1). Due to the limited number of patients, we were unable to identify any genotype–phenotype correlation.

In this study, patient 1 at 61 years of age presented clinical manifestations of the end stage of VWM, with completely vanishing white matter. We are unable to distinguish the border of periventricular zones in the brain MRI for this patient. Although patient 1 is now bedridden with no response or motor activity, the onset of her neurological symptoms began at age 29. Therefore, compared to the other patients, this patient showed later onset of disease and slower disease progression. The sibling case of patient 4 and 5 also showed late onset and slow progression, and only started to exhibit neurological symptoms after adolescence. In the early stage of VWM, brain MRI may not necessarily show diffuse cerebral white matter abnormalities and rarefaction or cystic degeneration [27]. Therefore, the brain MRI of patient 4 and 5, showing abnormal T2 high intensity only in the deep white matter, is suggestive of an early disease stage.

The other three patients (patient 2, 3, and 6) showed typical, diffuse white matter abnormalities in MRI. They started to show neurological symptoms during early infancy, and their disease occurrences were triggered by environmental factors (high fever due to infections) and were followed by episodes of acute deterioration associated with disturbed consciousness and seizures. These provocations have been frequently observed in VWM patients [11].

Because EIF2B is involved in regulating the first steps of protein synthesis and is ubiquitously expressed, it is unclear why EIF2B alterations cause a brain-specific disease [28,29]. Although many mutations identified in patients with VWM showed reduced EIF2B activities [30], basal activities *per se* do not explain the disease severity. Rather, the decreased EIF2B activity might impair the cellular stress response and improperly activate the unfolded protein response (UPR) leading to the endoplasmic reticulum (ER) stress [31]. The ER load in astrocytes and oligodendrocytes is possibly higher than in other cell types, rendering them vulnerable to conditions that predispose to ER stress [32,33]. This is the probable reason for disease provocations after environmental stress factors in patients with EIF2B alterations.

In this study, we recruited 22 patients who showed mimicking clinical manifestations of VWM. Among them, only six patients had genomic mutations in EIF2B genes. The final diagnosis of the other 16 patients is unknown at present. This would be challenges to be overcome in our future.

Acknowledgements

We would like to acknowledge the Collaborative Research Supporting Committee of the Japanese Society of Child Neurology (14-3) for promoting this study. This work was supported by a Grant-in-Aid for Scientific Research from Health Labor Sciences Research Grants from the Ministry of Health, Labor, and Welfare, Japan (T.Y.).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.braindev.2015.03.003.

References

[1] van der Knaap MS, Barth PG, Gabreels FJ, Franzoni E, Begeer JH, Stroink H, et al. A new leukoencephalopathy with vanishing white matter. Neurology 1997;48:845–55.
[2] Hanefeld F, Holzbach U, Kruse B, Wilichowski E, Christen HJ, Frahm J. Diffuse white matter disease in three children: an encephalopathy with unique features on magnetic resonance imaging and proton magnetic resonance spectroscopy. Neuropediatrics 1993;24:244–8.
[3] Schiffmann R, Moller JR, Trapp BD, Shih HH, Farrer RG, Katz DA, et al. Childhood ataxia with diffuse central nervous system hypomyelination. Ann Neurol 1994;35:331–40.
[4] Leegwater PA, Vermeulen G, Konst AA, Naidu S, Mulders J, Visser A, et al. Subunits of the translation initiation factor eIF2B are mutant in leukoencephalopathy with vanishing white matter. Nat Genet 2001;29:383–8.
[5] van der Knaap MS, Leegwater PA, Konst AA, Visser A, Naidu S, Oudejans CB, et al. Mutations in each of the five subunits of translation initiation factor eIF2B can cause leukoencephalopathy with vanishing white matter. Ann Neurol 2002;51:264–70.
[6] Pronk JC, van Kollenburg B, Scheper GC, van der Knaap MS. Vanishing white matter disease: a review with focus on its genetics. Ment Retard Dev Disabil Res Rev 2006;12:123–8.
[7] Maletkovic J, Schiffmann R, Gorospe JR, Gordon ES, Mintz M, Hoffman EP, et al. Genetic and clinical heterogeneity in eIF2B-related disorder. J Child Neurol 2008;23:205–15.
[8] Scali O, Di Perri C, Federico A. The spectrum of mutations for the diagnosis of vanishing white matter disease. Neurol Sci 2006;27:271–7.
[9] Matsui M, Mizutani K, Ohtake H, Miki Y, Ishizu K, Fukuyama H, et al. Novel mutation in EIF2B gene in a case of adult-onset leukoencephalopathy with vanishing white matter. Eur Neurol 2007;57:57–8.
[10] Horzinski L, Gonthier C, Rodriguez D, Scherer C, Boespflug-Tanguy O, Fogli A. Exon deletion in the non-catalytic domain of eIF2Bepsilon due to a splice site mutation leads to infantile forms of CACH/VWM with severe decrease of eIF2B GEF activity. Ann Hum Genet 2008;72:410–5.