様式第１９

学　会　等　発　表　実　績

委託業務題目「難治性てんかんを呈する稀少疾患群の遺伝要因と分子病態の解明に関する研究」

機関名　横浜市立大学

１．学会等における口頭・ポスター発表

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
Genetic analysis in infantile epileptic encephalopathies with movement disorder: a single center study.（口演）	Jun Tohyama, Noriyuki Akasaka, Yu Kobayashi, Shinichi Magara, Hideshi Kawashima, Mitsuhiro Kato, Naomichi Matsumoto, Hirotomo Saitsu	11th European Congress on Epileptology: Stockholm, Sweden	June 29 - July 3, 2014	国外
Epilepsy in *STXBP1* encephalopathy: Clinical delineation of 32 Japanese patients including 14 novel patients.　（ポスター）	M. Kato, H. Saitsu, H. Osaka, K. Nakamura, T. Watanabe, H. Terashima, T. Ikeda, T. Kumada, H. Matsumoto, T. Yamaguchi, J. Azuma, Y. Tominaga, M. Shinpoo, H. Arai, S. Hirai, S. Takeshita, E. Nakagawa, H. Uchio, Y. Nonoda, T. Iwasaki, T. Chiyonobu, A. Sudo, S. Kimura, Y. Takami, Y. Inaba, T. Wada, S. Kumada, M. Shimono, S. Miyama, K. Orii, N. Akasaka, J. Tohyama, M. Kubota, M. Nakashima, N. Matsumoto	American Epilepsy Society 2014, 68th Annual Meeting Seattle, USA	December 5-9, 2014	国外
Distinct Phenotypes And Genotypes Of SPTAN1 Encephalopathy.　（ポスター）	J. Tohyama, M. Nakashima, Z. Rener, Primec, C. Gaik-Siew, S. Nabatame, M. Kato, N. Matsumoto, H. Saitsu	American Epilepsy Society 2014, 68th Annual Meeting: Seattle, USA	December 5-9, 2014	国外
Sturge-Weber syndromeにおけるGNAQ体細胞変異の同定.　（口演）	中島光子、宮嶋雅一、新井一、加藤光広、松本直通	日本人類遺伝学会第59回大会・日本遺伝子診療学会第21回大会合同大	2014年11月20-22日	国内

		会：東京		
SCN8A の de novo 変異が原因となる乳児期早期発症の難治性てんかんについての検討. （口演）	大場ちひろ、加藤光広、高橋悟、寺嶋宙、久保田雅也、川脇壽、松藤まゆみ、小島泰子、舘野昭彦、中島光子、西山精視、鶴崎美徳、三宅紀子、田中章景、才津浩智、松本直通	日本人類遺伝学会第 59 回大会・日本遺伝子診療学会第 21 回大会合同大会：東京	2014 年 11 月 20-22 日	国内
PIK3R2 遺伝子変異を認めた Megalencephaly-polymicrogyria-polydactyly-hydrocephalus (MPPH) 症候群の軽症例. （ポスター）	露崎悠、佐藤睦美、渡辺肇子、安西理恵、市川和志、井合瑞江、山下純正、後藤知英、黒澤健司、中村和幸、加藤光広、才津浩智、松本直通	日本人類遺伝学会第 59 回大会・日本遺伝子診療学会第 21 回大会合同大会：東京	2014 年 11 月 20-22 日	国内
先天性糖鎖合成異常症の新規原因遺伝子 *COG2* の同定 （口演）	小寺啓文、安藤直樹、湯浅勲、和田芳直、鶴崎美徳、中島光子、三宅紀子、齋藤伸治、松本直通、才津浩智	日本人類遺伝学会第 59 回大会・日本遺伝子診療学会第 21 回大会合同大会：東京	2014 年 11 月 20-22 日	国内
TUBB4A 変異が引き起こす白質形成不全症の表現型の検討 （口演）	才津浩智、宮武聡子、小坂仁、椎名政昭、佐々木征行、高梨潤一、萩野谷和裕、和田敬仁、森本昌史、安藤直樹、生田陽二、中島光子、鶴崎美徳、三宅紀子、緒方一博、松本直通	日本人類遺伝学会第 59 回大会・日本遺伝子診療学会第 21 回大会合同大会：東京	2014 年 11 月 20-22 日	国内
てんかんで発症し、脳症様エピソードを経て著明な退行を示した SSADH 欠損症の一例. （ポスター）	石渡久子、鹿島田彩子、高橋孝治、黒神経彦、下平雅之、佐久間啓、才津浩智、加藤光広、菅原祐之	第 48 回日本てんかん学会年次学術集会：東京	2014 年 10 月 2-3 日	国内
A Newly identified congenital disorder of glycosylation caused by de novo mutations in *SLC35A2* encoding a UDP-galactose transporter is associated with early-onset epileptic encephalopathy. （口演）	中村 和幸、小寺 啓文、加藤 光広、小坂 仁、前垣 義弘、萩野谷 和裕、岡本 伸彦、井合 瑞江、才津 浩智、松本 直通	第 48 回日本てんかん学会年次学術集会：東京	2014 年 10 月 2-3 日	国内

WDR45 mutation causes static encephalopathy of childhood with neurodegeneration in adulthood (SENDA). (口演)	Kazuhiro Muramatsu, Satoko Kumada, Kenji Sugai, Emi Kasai-Yoshida, Noriko Sawaura ,Hiroya Nishida, Ai Hoshino, Fukiko Ryujin,Seiichirou Yoshioka, Mitsuhiro Kato, Hirokazu Arakawa '¥Hirotomo Saitsu c , Naomichi Matsumoto	第 56 回日本小児神経学会総会：浜松	2014 年 5 月 29 日-5 月 31 日	国内
SCN1A の変異を認めたてんかん性脳症の 1 男児例. (口演)	竹下美佳、山中岳、森地振一郎、石田悠、小穴信吾、宮島祐、河島尚志、才津浩智、加藤光広	第 56 回日本小児神経学会総会：浜松	2014 年 5 月 29 日-5 月 31 日	国内
KCNT1 遺伝子の新生変異が同定された West 症候群の女児例. (ポスター)	井上貴仁, 石井敦士, 鶴澤礼実, 中村紀子, 金海武志, 才津浩智, 加藤光広, 廣瀬伸一, 小川厚	第 56 回日本小児神経学会総会：浜松	2014 年 5 月 29 日-5 月 31 日	国内
West 症候群を発症した Potocki-Shaffer 症候群の一例. (口演)	高橋孝治、保立麻美子、馬場信平、中島啓介、鹿島田彩子、菅原祐之、加藤光広、才津浩智	第 56 回日本小児神経学会総会：浜松	2014 年 5 月 29 日-5 月 31 日	国内
SCN2A 変異を有し、特異な経過を辿ったてんかんの一例. (口演)	石渡久子、馬場信平、森山剣光、中島啓介、鹿島田彩子、加藤光広、中島光子、菅原祐之、岩川善英	第 61 回日本小児神経学会関東地方会学術集会：つくば	2014 年 9 月 20 日	国内

２．学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名	発表した場所（学会誌・雑誌等名）	発表した時期	国内・外の別
Early onset epileptic encephalopathy caused by de novo *SCN8A* mutations.	Ohba C, Kato M, Takahashi S, Lerman-Sagie T, Lev D, Terashima H, Kubota M, Kawawaki H, Matsufuji M, Kojima Y, Tateno A, Goldberg-Stern H, Straussberg R, Marom D, Leshinsky-Silver E, Nakashima M, Nishiyama K, Tsurusaki Y, Miyake N, Tanaka F, Matsumoto N, Saitsu H	*Epilepsia*	55:994-1000, 2014	国外

The somatic *GNAQ* mutation c.548G>A (p.R183Q) is consistently found in Sturge-Weber syndrome.	Nakashima M, Miyajima M, Sugano H, Iimura Y, Kato M, Tsurusaki Y, Miyake N, Saitsu H, Arai H, Matsumoto N	*J Hum Genet*	59:691-3, 2014	国外
Novel compound heterozygous *PIGT* mutations caused multiple congenital anomalies-hypotonia-seizures syndrome 3.	Nakashima M, Kashii H, Murakami Y, Kato M, Tsurusaki Y, Miyake N, Kubota M, Kinoshita T, Saitsu H, Matsumoto N	*Neurogenetics*	15:193-200, 2014	国外
AKT3 and *PIK3R2* mutations in two patients with megalencephaly-related syndromes: MCAP and MPPH.	Nakamura K, Kato M, Tohyama J, Shiohama T, Hayasaka K, Nishiyama K, Kodera H, Nakashima M, Tsurusaki Y, Miyake N, Matsumoto N, Saitsu H	*Clin Genet*	85:396-8, 2014	国外
Is focal cortical dysplasia sporadic? Family evidence for genetic susceptibility.	Leventer RJ, Jansen FE, Mandelstam SA, Ho A, Mohamed I, Sarnat HB, Kato M, Fukasawa T, Saitsu H, Matsumoto N, Itoh M, Kalnins RM, Chow CW, Harvey AS, Jackson GD, Crino PB, Berkovic SF, Scheffer IE	*Epilepsia*	55:e22-6, 2014	国外
PIGA mutations cause early-onset epileptic encephalopathies and distinctive features.	Kato M, Saitsu H, Murakami Y, Kikuchi K, Watanabe S, Iai M, Miya K, Matsuura R, Takayama R, Ohba C, Nakashima M, Tsurusaki Y, Miyake N, Hamano S, Osaka H, Hayasaka K, Kinoshita T, Matsumoto N	*Neurology*	82:1587-96, 2014	国外
A girl with West syndrome and autistic features harboring a *de novo TBL1XR1* mutation.	Saitsu H, Tohyama J, Walsh T, Kato M, Kobayashi Y, Lee M, Tsurusaki Y, Miyake N, Goto Y, Nishino I, Ohtake A, King MC, Matsumoto N	*J Hum Genet*	59:581-3, 2014	国外
Mutations in the glutaminyl-tRNA synthetase gene cause early-onset epileptic	Kodera H, Osaka H, Iai M, Aida N, Yamashita A, Tsurusaki Y, Nakashima M, Miyake N, Saitsu H,	*J Hum Genet*	60:97-101, 2015	国外

encephalopathy.	Matsumoto N.			
Compound heterozygous *BRAT1* mutations cause familial Ohtahara syndrome with hypertonia and microcephaly.	Saitsu H, Yamashita S, Tanaka Y, Tsurusaki Y, Nakashima M, Miyake N, Matsumoto N.	*J Hum Genet*	59:687-90, 2014	国外
Causative novel *PNKP* mutations and concomitant *PCDH15* mutations in a patient with microcephaly with early-onset seizures and developmental delay syndrome and hearing loss.	Nakashima M, Takano K, Osaka H, Aida N, Tsurusaki Y, Miyake N, Saitsu H, Matsumoto N.	*J Hum Genet*	59:471-4, 2014	国外
De novo SOX11 mutations cause Coffin-Siris syndrome.	Tsurusaki Y, Koshimizu E, Ohashi H, Phadke S, Kou I, Shiina M, Suzuki T, Okamoto N, Imamura S, Yamashita M, Watanabe S, Yoshiura K, Kodera H, Miyatake S, Nakashima M, Saitsu H, Ogata K, Ikegawa S, Miyake N, Matsumoto N.	*Nat Commun.*	2;5:4011, 2014	国外
Expanding the phenotypic spectrum of *TUBB4A*-associated hypomyelinating leukoencephalopathies.	Miyatake S, Osaka H, Shiina M, Sasaki M, Takanashi J, Haginoya K, Wada T, Morimoto M, Ando N, Ikuta Y, Nakashima M, Tsurusaki Y, Miyake N, Ogata K, Matsumoto N, Saitsu H.	*Neurology*	82:2230-7, 2014	国外
Paternal germline mosaicism of a *SCN2A* mutation results in Ohtahara syndrome in half siblings.	Zerem A, Lev D, Blumkin L, Goldberg-Stern H, Michaeli-Yossef Y, Halevy A, Kivity S, Nakamura K, Matsumoto N, Leshinsky-Silver E, Saitsu H, Lerman-Sagie T.	*Eur J Paediatr Neurol.*	18:567-71, 2014	国外
Mutations in *COG2* Encoding a Subunit of the Conserved Oligomeric Golgi Complex Cause a Congenital Disorder of	Kodera H, Ando N, Yuasa I, Wada Y, Tsurusaki Y, Nakashima M, Miyake N, Saitoh S, Matsumoto N, Saitsu H.	*Clin Genet.*	2014, [Epub ahead of print]	国外

Glycosylation.				
Infantile epileptic encephalopathy with a hyperkinetic movement disorder and hand stereotypies associated with a novel SCN1A mutation.	Ohashi T, Akasaka N, Kobayashi Y, Magara S, Kawashima H, Matsumoto N, Saitsu H, Tohyama J.	*Epileptic Disord.*	16:208-12, 2014	国外
De novo *EEF1A2* mutations in patients with characteristic facial features, intellectual disability, autistic behaviors and epilepsy.	Nakajima J, Okamoto N, Tohyama J, Kato M, Arai H, Funahashi O, Tsurusaki Y, Nakashima M, Kawashima H, Saitsu H, Matsumoto N, Miyake N.	*Clin Genet.*	2014, [Epub ahead of print]	国外
De novo *WDR45* mutation in a patient showing clinically Rett syndrome with childhood iron deposition in brain.	15. Ohba C, Nabatame S, Iijima Y, Nishiyama K, Tsurusaki Y, Nakashima M, Miyake N, Tanaka F, Ozono K, Saitsu H, Matsumoto N.	*J Hum Genet*	59:292-5, 2014	国外
PIGO mutations in intractable epilepsy and severe developmental delay with mild elevation of alkaline phosphatase levels.	Nakamura K, Osaka H, Murakami Y, Anzai R, Nishiyama K, Kodera H, Nakashima M, Tsurusaki Y, Miyake N, Kinoshita T, Matsumoto N, Saitsu H.	*Epilepsia*	55(2):e13-7, 2014	国外
PIGN mutations cause congenital anomalies, developmental delay, hypotonia, epilepsy, and progressive cerebellar atrophy. Neurogenetics.	Ohba C, Okamoto N, Murakami Y, Suzuki Y, Tsurusaki Y, Nakashima M, Miyake N, Tanaka F, Kinoshita T, Matsumoto N, Saitsu H.	*Neurogenetics.*	15(2):85-92, 2014	国外

様式第１９

学　会　等　発　表　実　績

委託業務題目「難治性てんかんを呈する稀少疾患群の遺伝要因と分子病態の解明に関する研究」

機関名　国立大学法人浜松医科大学

１．学会等における口頭・ポスター発表

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
Prenatal stress-induced selective deterioration of neurogenesis of parvalbuminpositive GABAergic neurons.　（口頭）	Fukuda, A.	第92回日本生理学会大会 シンポジウム " Recent findings in development, function and disease of GABAergic neurons"	3/23, 2015.	国内
Functional regulation of neuronal K+-Cl - cotransporter KCC2.　（口頭）	Watanabe, M., Iwata, S., Furukawa, T., Kumada, T., Uchida, T., Hirose, S. and Fukuda, A.	第92回日本生理学会大会　シンポジウム " Morphological and functional mechanisms and their dynamics in the multimodality of inhibitory neural system"	3/23, 2015.	国内
母体由来タウリンが胎仔脳の形成とその特異性に与える影響.　（口頭）	古川智範，福田敦夫	第41回日本脳科学会	11/22, 2014.	国内
Alterlations in extracellular sugar chain in prenatally stressed mouse brain.　（ポスター）	Fukuda, A. and Wang, T.	SFG & JSCR 2014 Joint Annual Meeting Satellite Symposium II: "Glycans in Neuroscience"	11/16, 2014.	国外
GAD67-GFP knockinマウスを用いた CRH ニューロン制御における GABA の役割についての検討.　（口頭）	柿沢圭亮，渡部美穂，柳川右千夫，沖隆，福田敦夫.	第61回中部日本生理学会	11/7, 2014.	国内
発達期のマルチモーダルな GABA 受容体作用から麻酔薬毒性を考察する.　（口頭）	福田敦夫	第34回日本臨牀麻酔学会 シンポジウム17　発達期脳に対する麻酔薬の毒性、最新の知見 —基礎から今日の臨床をどうするか—	11/2, 2014.	国内

GAD67-GFP ノックインマウスを用いた CRH ニューロン制御における GABA の役割についての検討. （口頭）	柿沢圭亮，渡部美穂，大川雄太，大石敏弘，山下美保，柳川右千夫，沖 隆，福田敦夫.	第 41 回日本神経内分泌学会学術集会	11/1, 2014.	国内
Maternally-derived ambient taurine plays a pivotal role in radial migration in the embryonic mouse neocortex by tonically activating $GABA_A$ receptors. （口頭）	Fukuda, A., Furukawa, T., Yamada, J., Akita, T., Matsushima, Y., Yanagawa, Y.	第 37 回日本神経科学大会	9/12, 2014.	国内
Maternal taurine modulates immature aspect of GABA actions involved in epileptogenesis. （口頭）	Fukuda, A.	The 16th Annual Meeting of Infantile Seizure Society (ISS): International Symposium on Epileptic Syndromes of Early Infancy and Childhood (ISES)	6/23, 2014.	国外

２．学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名	発表した場所（学会誌・雑誌等名）	発表した時期	国内・外の別
KCC2-mediated regulation of respiration-related rhythmic activity during postnatal development in mouse medulla oblongata.	Okabe, A., Shimizu-Okabe, C., Arata, A., Konishi, S., Fukuda, A. and Takayama, C.	Brain Res 1601:31-39	2015	国外
Activity-dependent endogenous taurine release facilitates excitatory neurotransmission in the neocortical marginal zone of neonatal rats.	Qian, T., Chen, R., Nakamura, M., Furukawa, T., Kumada, T., Akita, T., Kilb, W., Luhmann, H. J., Nakahara, D., and *Fukuda, A.	Front. Cell. Neurosci. 8:33,	2014	国外
Activation of glycine receptors modulates spontaneous epileptiform activity in the immature rat hippocampus.	Chen, R., Okabe, A., Sun, H., Sharopov, S., Hanganu-Opatz, I.L., Kolbaev, S.N., Fukuda, A., Luhmann, H.J., Kilb, W.	J Physiol 592:2153-2168	2014	国外
Roles of taurine-mediated tonic GABAA-receptor activation in radial migration of neurons in	Furukawa, T., Yamada, J., Akita, T., Matsushima, Y., Yanagawa, Y., *Fukuda, A.	Front Cell Neurosci 8:88	2014	国外

the developing cerebral cortex.				
Selective loss of parvalbumin-positive GABAergic interneurons in the cerebral cortex of maternally stressed Gad1-heterozygous mouse offspring.	Uchida, T., Furukawa, T., Iwata, S., Yanagawa, Y., *Fukuda, A.	Transl Psychiatry 4 e371	2014	国外
Accumulation of GABAergic neurons, causing a focal ambient GABA gradient, and downregulation of KCC2 are induced during microgyrus formation in a mouse model of polymicrogyria.	Wang, T., Kumada, T., Morishima, T., Iwata, S., Kaneko, T., Yanagawa, Y., Yoshida, S. and *Fukuda, A.	Cereb. Cortex 24:1088-1101	2014	国外
Functional deficiency of MHC class I enhances LTP and abolishes LTD in the nucleus accumbens of mice.	Edamura, M., Murakami, G., Meng, H., Itakura, M., Shigemoto R., Fukuda, A. and Nakahara, D.	PLoS ONE 9:107099	2014	国外

様式第１９

学　会　等　発　表　実　績

委託業務題目「難治性てんかんを呈する稀少疾患群の遺伝要因と分子病態の解明に関する研究」

機関名　国立大学法人新潟大学

１．学会等における口頭・ポスター発表

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
Different mechanism of epileptogensis in subiculum and dentate gyrus in mesial temporal lobe epilepsy: an in vitro optical imaging study of resected human hippocampus	Hiroki Kitaura, Hiroshi Shirozu, Hiroshi Shimizu, Masaki Sonoda, Hiroatsu Murakami, Hiroshi Masuda, Hitoshi Takahashi, Shigeki Kameyama, Akiyoshi Kakita	Society for Neuroscience	2014年11月	国外
てんかん焦点の病理	柿田明美	第48回日本てんかん学会	2014年10月	国内
視床下部過誤腫の生検組織スライス標本を用いた生理学的・薬理学的研究	園田真樹、北浦弘樹、伊藤陽祐、白水洋史、増田浩、柿田明美、亀山茂樹	第49回日本てんかん学会	2014年11月	国内
内側側頭葉てんかん患者の海馬萎縮:VBMによるMRI解析と病理所見との比較研究	伊藤陽祐、増田浩、白水洋史、村上博淳、園田真樹、亀山茂樹、北浦弘樹、高橋均、柿田明美	第48回日本てんかん学会	2014年10月	国内
限局性皮質形成異常によるてんかん患者の発作頻度の特徴について	跡部真人，須貝研司，石山昭彦，齋藤貴志，斎藤義朗，小牧宏文，中川栄二，佐々木征行，高橋章夫，大槻泰介，伊藤雅之，柿田明美	第56回日本小児神経学会	2014年5月	国内
ヒトてんかん病巣におけるグリア細胞の病理組織学的所見	柿田明美	第55回日本神経学会	2014年5月	国内
視床下部過誤腫におけるてんかん原性のin vitro脳スライス標本を用いた検討	北浦弘樹、園田真樹、清水宏、白水洋史、伊藤陽祐、増田浩、高橋均、亀山茂樹、柿田明美	第55回日本神経病理学会	2014年6月	国内
内側側頭葉てんかん患者の海馬硬化組織特異的な酸化損傷タンパクの同定	古川絢子、柿田明美、千葉陽一、樋口善博、高橋均、亀山茂樹、島田厚良	第55回日本神経病理学会	2014年6月	国内
内側側頭葉てんかんにおける臨床病理学的研究	塩谷彩子、大槻泰介、佐々木征行、佐藤典子、柿田明美、齊藤祐子	第55回日本神経病理学会	2014年6月	国内
*L1CAM*遺伝子変異を伴う伴性劣性遺伝性水頭症の胎児例	清水宏、花岡仁一、金村米博、山崎麻美、田澤立之、高橋均、柿田明美	第55回日本神経病理学会	2014年6月	国内

２．学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名	発表した場所（学会誌・雑誌等名）	発表した時期	国内・外の別
Characteristic p57/Kip2 immunoreactivity of balloon cells in focal cortical dysplasia.	Kimura T, Kitaura H, Masuda H, Kameyama S, Saito Y, Otsuki T, Nakazawa A, Morota N, Yamamoto T, Iida K, Takahashi H, Kakita A.	Neuropathology	in press	国内
Two siblings with cortical dysplasias: focal cortical dysplasia and hemimegalencephaly: clinicoencephalographic features.	Fukasawa T, Kubota T, Negoro T, Maruyama S, Honda R, Saito Y, Ito M, Kakita A, Sugai K, Otsuki T, Natsume J, Watanabe K.	Pediatr Int	in press	国内
ヒトてんかん病巣におけるグリア細胞の病理組織学的所見	柿田明美	臨床神経 2014; 54(12): 1136-1157.	2014年12月	国内
小児てんかん原性病巣の外科病理	柿田明美	脳発達 2014; 46(6): 413-417.	2014年11月	国内

様式第１９

学　会　等　発　表　実　績

委託業務題目「難治性てんかんを呈する稀少疾患群の遺伝要因と分子病態の解明に関する研究」

機関名　国立病院機構西新潟中央病院

１．学会等における口頭・ポスター発表

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
Genetic analysis in infantile epileptic encephalopathies with movement disorder: a single center study（口頭）	Tohyama J, Akasaka N, Kobayashi Y, Magara S, Kawashima H, Kato M, Matsumoto N, Saitsu H.	ストックホルム,スエーデン（第11回ヨーロッパてんかん学会）	2014.7.1	国外
Distinct phenotypes and genotypes of SPTAN1 encephalopathy（ポスター発表）	Tohyama J, Nakashima M, Rener-Primec Z, Gaik-Siew C, Nabatame S, Kato M, Matsumoto N, Saitsu H.	シアトル,アメリカ合衆国（第68回アメリカてんかん学会）	2014.12.6	国外
Megalencephaly-polymicrogyria-polydactyly-hydrocephalus (MPPH) 症候群症例の長期経過.（口頭）	遠山　潤，赤坂紀幸，小林　悠，眞柄慎一，川島英志，中村和幸，加藤光広，松本直通，才津浩智.	名古屋市（第37回日本小児遺伝学会）	2014.4.10	国内
小児てんかん発作と鑑別診断（口頭）	遠山　潤	東京都（第48回日本てんかん学会総会）	2014.10.3	国内
新潟県での小児てんかん診療連携の実際と課題 -Dravet 症候群症例を通して-.	遠山　潤，赤坂紀幸，小林　悠，眞柄慎一，川島英志.	東京都(第2回全国てんかんセンター協議会総会)	2015.2.15	国内
当院における Rufinamide の使用経験（口頭）	川島英志，遠山　潤，赤坂紀幸，小林悠，眞柄慎一，増田浩，白水洋史，笹川睦男	浜松市（第56回日本小児神経学会総会）	2014.5.30	国内
傾斜磁場トポグラフィーを用いた遅発型小児後頭葉てんかん（Gastaut 型）の脳磁図解析（口頭）	眞柄慎一，白水洋史，川島英志，小林悠，赤坂紀幸，遠山　潤	浜松市（第56回日本小児神経学会総会）	2014.5.30	国内
Gómez López-Hernández 症候群の一例（ポスター）	小林悠，川島英志，眞柄慎一，赤坂紀幸，遠山　潤	Gómez López-Hernández syndrome	2014.5.29	国内
小児難治てんかんにおけるレベチラセタムの有効性と忍容性の検討(口頭)	赤坂紀幸，川島英志，眞柄慎一，小林悠，遠山　潤	東京都（第48回日本てんかん学会総会）	2014.10.3	国内
てんかんを合併した結節性硬化症の予後についての検討（ポスター）	川島英志，遠山　潤，赤坂紀幸，小林悠，眞柄慎一，増田浩，笹川睦男，亀山茂樹，	東京都（第48回日本てんかん学会総会）	2014.10.2	国内
FOXG1 を含む14番染色体長	眞柄慎一，遠山　潤，川	東京都（第48回日	2014.10.	国内

腕部分トリソミーモザイク2症例の臨床像（ポスター）	島英志，小林悠，赤坂紀幸，山本俊至，齋藤伸治	本てんかん学会総会）	3	
てんかんが自閉的特性に及ぼす後天的影響（ポスター）	長谷川直哉，遠山　潤，亀山茂樹	東京都（第48回日本てんかん学会総会）	2014.10.3	国内
古典的非ケトン性高グリシン血症に対するケトンミルク療法の経験(口頭)	眞柄慎一，川島英志，小林悠，赤坂紀幸，遠山潤，小嶋絹子	安曇野市（第18回日本小児神経学会甲信越地方会）	2014.10.25	国内

2．学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名	発表した場所（学会誌・雑誌等名）	発表した時期	国内・外の別
Infantile epileptic encephalopathy with a hyperkinetic movement disorder and hand stereotypies associated with a novel SCN1A mutation.	Ohashi T, Akasaka N, Kobayashi Y, Magara S, Kawashima H, Matsumoto N, Saitsu H, Tohyama J.	Epileptic Disorders	2014年4月	国外
Gómez López-Hernández syndrome in a Japanese patient: A case report.	Kobayashi Y, Kawashima H, Magara S, Akasaka N, Tohyama J.	Brain and Development	2015年3月	国外
De novo EEF1A2 mutations in patients with characteristic facial features, intellectual disability, autistic behaviors and epilepsy.	Nakajima J, Okamoto N, Tohyama J, Kato M, Arii H, Funahashi O, Tsurusaki Y, Namashima M, Kawashima H, Saitsu H, Matsumoto N, Miyake N.	Clinical Genetics	2014年4月	国外
A girl with West syndrome and autistic features harboring a de novo TBL1XR1 mutation.	Saitsu H, Tohyama J, Walsh T, Kato M, Kobayashi Y, Lee M, Tsurusaki Y, Miyake N, Goto Y, Nishini I, Ohtake A, King MC, Matsumoto N.	Journal of Human Genetics	2014年10月	国外
Prenatal molecular diagnosis of X-linked hydrocephalus via a silent C924T mutation in the L1CAM gene.	Serikawa T, Nishiyama K, Tohyama J, Tazawa R, Goto K, Kuriyama Y, Haino K, Kanemura Y, Yamasaki M, Nakata K, Takakuwa K, Enomoto T.	Congenital Anomaly	2014年11月	国内
SPTAN1 encephalopathy: distinct phenotypes and genotypes.	Tohyama J, Nakashima M, Nabatame S, Gaik-Siew C, Miyata R, Rener-Primec Z, Kato M, Matsumoto N, Saitsu H.	Journal of Human Genetics	2015年1月	国外
Rub epilepsy in an infant with Turner syndrome.	Magara S, Kawashima H, Kobayashi Y, Akasaka N,	Brain and Development	2014年12月	国外

	Yamazaki S, Tohyama J.			
新生児けいれんを伴う先天代謝異常.	遠山　潤	神経症候群（第2版）VI,	2014年12月	国内

Ⅳ. 研究成果の刊行物・別刷

FULL-LENGTH ORIGINAL RESEARCH

Early onset epileptic encephalopathy caused by de novo *SCN8A* mutations

*†Chihiro Ohba, ‡Mitsuhiro Kato, §Satoru Takahashi, ¶Tally Lerman-Sagie, #Dorit Lev, **Hiroshi Terashima, **Masaya Kubota, ††Hisashi Kawawaki, ‡‡Mayumi Matsufuji, §§Yasuko Kojima, §§Akihiko Tateno, ##Hadassa Goldberg-Stern, ##Rachel Straussberg, ##Dafna Marom, ***Esther Leshinsky-Silver, *Mitsuko Nakashima, *Kiyomi Nishiyama, *Yoshinori Tsurusaki, *Noriko Miyake, †Fumiaki Tanaka, *Naomichi Matsumoto, and *Hirotomo Saitsu

Epilepsia, **(*):1–7, 2014
doi: 10.1111/epi.12668

Chihiro Ohba, a neurologist, is interested in genetic factors causing neuro-developmental disorders.

Summary

Objective: **De novo *SCN8A* mutations have been reported in patients with epileptic encephalopathy. Herein we report seven patients with de novo heterozygous *SCN8A* mutations, which were found in our comprehensive genetic analysis (target capture or whole-exome sequencing) for early onset epileptic encephalopathies (EOEEs).**

Methods: **A total of 163 patients with EOEEs without mutations in known genes, including 6 with malignant migrating partial seizures in infancy (MMPSI), and 60 with unclassified EOEEs, were analyzed by target capture (28 samples) or whole-exome sequencing (135 samples).**

Results: **We identified de novo *SCN8A* mutations in 7 patients: 6 of 60 unclassified EOEEs (10.0%), and one of 6 MMPSI cases (16.7%). The mutations were scattered through the entire gene: four mutations were located in linker regions, two in the fourth transmembrane segments, and one in the C-terminal domain. The type of the initial seizures was variable including generalized tonic–clonic, atypical absence, partial, apneic attack, febrile convulsion, and loss of tone and consciousness. Onset of seizures was during the neonatal period in two patients, and between 3 and 7 months of age in five patients. Brain magnetic resonance imaging (MRI) showed cerebellar and cerebral atrophy in one and six patients, respectively. All patients with *SCN8A* missense mutations showed initially uncontrollable seizures by any drugs, but eventually one was seizure-free and three were controlled at the last examination. All patients showed developmental delay or regression in infancy, resulting in severe intellectual disability.**

Significance: **Our data reveal that *SCN8A* mutations can cause variable phenotypes, most of which can be diagnosed as unclassified EOEEs, and rarely as MMPSI. Together with previous reports, our study further indicates that genetic testing of *SCN8A* should be considered in children with unclassified severe epilepsy.**

KEY WORDS: *SCN8A*, De novo mutation, Early onset epileptic encephalopathies.

Accepted April 22, 2014.

*Department of Human Genetics, Graduate School of Medicine, Yokohama City University, Yokohama, Japan; †Department of Clinical Neurology and Stroke Medicine, Yokohama City University, Yokohama, Japan; ‡Department of Pediatrics, Yamagata University Faculty of Medicine, Yamagata, Japan; §Department of Pediatrics, Asahikawa Medical University, Asahikawa, Japan; ¶Pediatric Neurology Unit, Wolfson Medical Center, Holon, Israel; #Metabolic Neurogenetic Clinic, Wolfson Medical Center, Holon, Israel; **Division of Neurology, National Center for Child Health and Development, Tokyo, Japan; ††Department of Pediatric Neurology, Osaka City General Hospital, Osaka, Japan; ‡‡Department of Pediatrics, Japan Community Health Care Organization Kyusyu Hospital, Kitakyushu, Japan; §§Department of Pediatrics, Toho University Sakura Medical Center, Chiba, Japan; ##Department of Neurogenetics, Schneider's Children Medical Center, Petah Tiqwa, Israel; and ***Institute of Medical Genetics, Wolfson Medical Center, Holon, Israel

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

Voltage-gated sodium channels (VGSCs) play important roles in initiation and propagation of action potentials.[1,2] VGSCs consist of one pore-forming α-subunit and one or two β-subunits.[1,2] The α-subunit is made up of four domains (domains I–IV), each containing a motif of six transmembrane segments (S1–S6). The fourth segment (S4) of each domain is positively charged for voltage sensing.[1,3] The VGSC repertoire in humans includes nine α subunits ($Na_v1.1$–$Na_v1.9$), of which $Na_v1.1$, $Na_v1.2$, and $Na_v1.3$, encoded by *SCN1A*, *SCN2A*, and *SCN3A*, respectively, are highly expressed in the brain[4] and when mutated can cause epilepsy.[3,5]

Na_v 1.6, encoded by *SCN8A*, is a major α-subunit in excitatory neurons of the central and peripheral nervous systems, and concentrates in the soma, axon initial segments, dendrites, and nodes of Ranvier.[2,6–8] Recently, a de novo *SCN8A* mutation, which results in a dramatic increase in persistent sodium current and incomplete channel inactivation, was identified in a patient with an infantile epileptic encephalopathy who died of sudden unexplained death in epilepsy (SUDEP).[9] Other de novo *SCN8A* mutations were found in a patient with intellectual disability and tonic–clonic seizures, and another patient with epileptic encephalopathy,[10–13] suggesting that *SCN8A* mutations are involved in epileptic encephalopathies.[8]

In this study, we performed target capture sequencing or whole-exome sequencing to elucidate the genetic basis of early onset epileptic encephalopathies (EOEEs). We identified de novo *SCN8A* mutations in seven patients with severe epileptic encephalopathies.

Patients and Methods

Patients

A total of 163 patients with EOEEs (48 patients with Ohtahara syndrome, 2 with early myoclonic encephalopathy, 47 with West syndrome, 6 with malignant migrating partial seizures in infancy [MMPSI], and 60 with unclassified EOEEs) were analyzed by target capture sequencing (28 samples) or whole-exome sequencing (135 samples). A total of 98 patients with mutations in *STXBP1*, *ARX*, *KCNQ2*, *SCN1A*, *SCN2A*, *KCNT1*, *CDKL5*, *CASK*, or *MECP2*, which were detected either by high resolution melting analysis, direct sequencing analysis, target capture sequencing, or whole-exome sequencing, were excluded from the study. Therefore, in 163 patients, mutations in the genes described were excluded except for 28 patients examined with target capture sequencing (*KCNT1* was not included in the captured probes used). The diagnosis was made by the clinical features and electroencephalography (EEG) patterns. The experimental protocols were approved by the institutional review board of Yokohama City University School of Medicine and Yamagata University Faculty of Medicine. Peripheral blood samples were obtained from family members after obtaining their written informed consent. Detailed clinical information was obtained from corresponding clinicians.

Target capture sequencing

A custom-made SureSelect oligonucleotide probe library (Agilent Technologies, Santa Clara, CA, U.S.A.) was designed to capture the coding exons of 50 genes, in which additional 15 genes, including *SCN8A*, were added to the panel of the previous 35 genes.[14] A total of 4,764 probes, covering 267 kb, were prepared. Twenty-four captured libraries were mixed and sequenced by the multiplex method on an Illumina MiSeq (Illumina, San Diego, CA, U.S.A.) with 150-bp paired-end reads. Data processing, variant calling, and variant annotation were performed as previously described.[14]

Whole-exome sequencing

Genomic DNA was captured using the SureSelect Human All Exon v4 Kit (51 Mb; Agilent Technologies) and sequenced on an Illumina HiSeq2000 (Illumina) with 101 bp paired-end reads. Four samples were run in one lane of the flow cell. Exome data processing, variant calling, and variant annotation were performed as described previously.[15]

Sanger sequencing

SCN8A mutations identified by target capture sequencing or whole-exome sequencing were confirmed by Sanger sequencing. Parental samples were sequenced to confirm whether parents possessed *SCN8A* mutations.

Results

A total of 7 *SCN8A* mutations were found in 7 patients: 6 of 60 unclassified EOEEs (10.0%), and one of 6 MMPSI cases (16.7%; Table 1). One mutation was identified by target capture sequencing and the other six mutations were found by whole-exome sequencing. They are absent from the 6,500 exomes included in the National Heart, Lung, and Blood Institute exome project and from our 408 in-house control exomes. Sorting Intolerant from Tolerant (SIFT), Polyphen2, and Mutation Taster predicted that the seven mutations were highly damaging to the structure of $Na_v1.6$, and all the seven mutations occurred at evolutionally conserved amino acids (Fig. S1 and Table S1). Two mutations occurred within the same amino acid residue (p.Asn1466): c.4398C>A (p.Asn1466Lys) in patient 1 and c.4397A>C (p.Asn1466Thr) in patient 5 (Fig. 1 and Table 1). The mutations were scattered throughout the entire gene: two in the inactivation gate between domains III and IV, one in a linker between S3 and S4 of domain I, one in S4 of domain II, one in S4 of domain IV, one in a linker between S4 and S5 of domain IV, and one in the C-terminal domain (Fig. 1).

Table 1. Clinical features of patients with *SCN8A* mutations

Clinical Feature	Patient number 1	2	3	4	5	6	7
Age	6 years	13 years	5 years	2 years	6 years	1 year 1 month	1 year 4 months
Sex	Male	Female	Male	Female	Male	Female	Male
Race	Japanese	Japanese	Japanese	Japanese	Israeli	Israeli	Israeli
Diagnosis	EOEE	EOEE	MMPSI	EOEE	EOEE	EOEE	EOEE
Mutation	c.4398C>A (p.Asn1466Lys)	c.647T>A (p.Val216Asp)	c.2537T>C (p.Phe846Ser)	c.4850G>A (p.Arg1617Gln)	c.4397A>C (p.Asn1466Thr)	c.5614C>T (p.Arg1872Trp)	c.4948G>A (p.Ala1650Thr)
Family history	–	–	+	–	+	–	–
Initial symptoms	Seizure	Seizure	Tachypnea and jitteriness (tremor)	Seizure	Seizure	Seizure	Seizure
Age at onset	3 days	7 months	0 days	3 months	4 months	3 months	3.5 months
Epilepsy	Tonic–clonic seizure	Absence seizure	Apneic attacks since 2 months, hemiclonic convulsions propagating to the other side since 4 months	FC at 3 months, tonic–clonic seizure at 6 months	PS with generalization at 4 month, focal tonic and generalized clonic seizures at 1 year, FS with generalization at 5 year	Prolonged tonic–clonic seizure since 3 months	Seizure manifesting as loss of tone and consciousness at 3.5 months, tonic seizure at 5.5 months
Initial EEG	Irregular polyspike-and-slow wave complexes	Focal spikes and 3 Hz generalized spike-and-wave burst	Normal at birth. At 4 months, polyspikes and migrating spike-and-slow wave complex	Normal at 3 months	Normal at 4 months, bilateral temporal sharp waves at 5 months	Multifocal spikes with bilateral discharges	Normal at 5.5 months
Response to therapy	Intractable, PHT+GBP, ACTH, TPM, MDL, LD temporarily effective	Intractable. Seizure-free from 6 years with VPA (now 13 years old)	Intractable, high-dose PB, PHT, LTG, KD, VNS temporarily effective	Intractable CBZ temporarily effective	Intractable, Controlled with TPM and CBZ	Intractable, Controlled with KD+TPM+LCM+LEV+VGB	Intractable, Controlled with TPM and CBZ
Initial motor development	Delayed	Delayed	Delayed	Delayed	Normal	Delayed	Normal
Development	Severely delayed	Severely delayed	Severely delayed	Severely delayed	Regressed	Severely delayed	Severely regressed
Hypotonia	+ (severe)	+ (5 months)	+	–	–	+	–
Intellectual disability	+ (profound)	+	+ (profound)	+ (profound)	+ (profound)	+ (profound)	+
Behavioral anomalies	+	+	–	–	+	–	–
Current status	Bedridden	Wheelchair	Bedridden	Sitting/crawling	Walking	Unable to sit or crawl, but able to roll over	Bedridden
MRI	MA of CB at 6 months, HI on T2WI in bilateral striatal bodies and occipital cortex	MA of frontal and temporal lobe at 1 year and 10 months	Normal at 0 and 2 months. MA of the CB and thin CC at 9 months and 4 years. MA of the cerebellum at 4 years	Normal at 6 months and 2 years	Normal at 8 months, diffuse brain atrophy at 1 year	Within normal limits, MA	Asymmetric ventricles at 3.5 months, mild diffuse atrophy at 12 months

EOEE, early–onset epileptic encephalopathies; MMPSI, malignant migrating partial seizures in infancy; FC, febrile convulsion; PS, partial seizure; FS, focal seizure; PHT, phenytoin; GBP, gabapentin; ACTH, adrenocorticotrophic hormone; TPM, topiramate; MDL, midazolam; LD, lidocaine; VPA, valproic acid; PB, phenobarbital; LTG, lamotrigine; KD, ketogenic diet; VNS, vagal nerve stimulation; CBZ, carbamazepine; LCM, lacosamide; LEV, levetiracetam; VGB, vigabatrin; HI, hyperintensity; T2WI, T_2-weighted image; MA, mild atrophy; CB, cerebrum; CC, corpus callosum; N.D., not described.

Epilepsia, **(*):1–7, 2014
doi: 10.1111/epi.12668

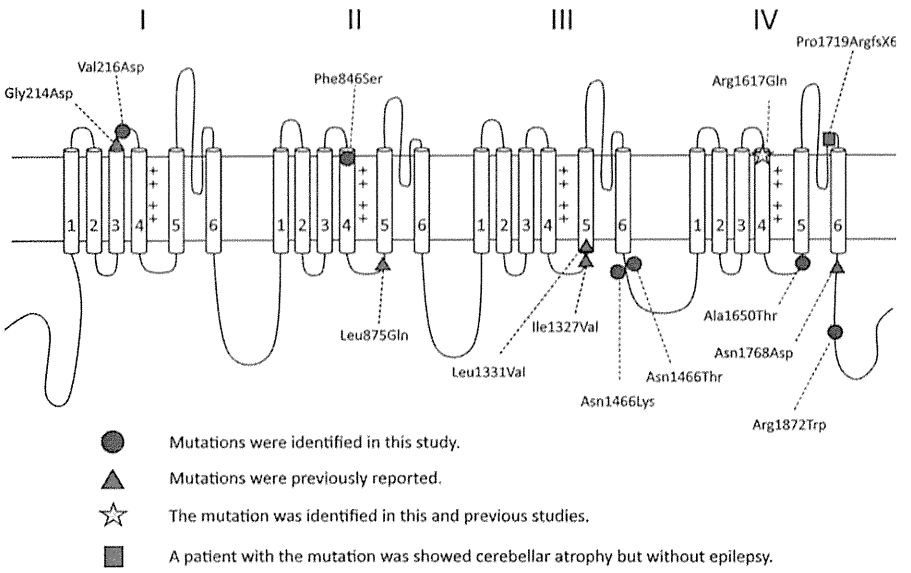

Figure 1.
Structure of the human $Na_v1.6$ channel showing location of *SCN8A* mutations. Mutation annotations are based on NM_014191.3. p.Gly214Asp, p.Leu875Gln, p.Ile1327Val, p.Leu1331Val, p.Arg1617Gln, p.Pro1719ArgfsX6, and p.Asn1768Asp were reported previously.[9–13,25] The patient with p.Pro1719ArgfsX6 showed cerebellar atrophy but without epilepsy.[25]
Epilepsia © ILAE

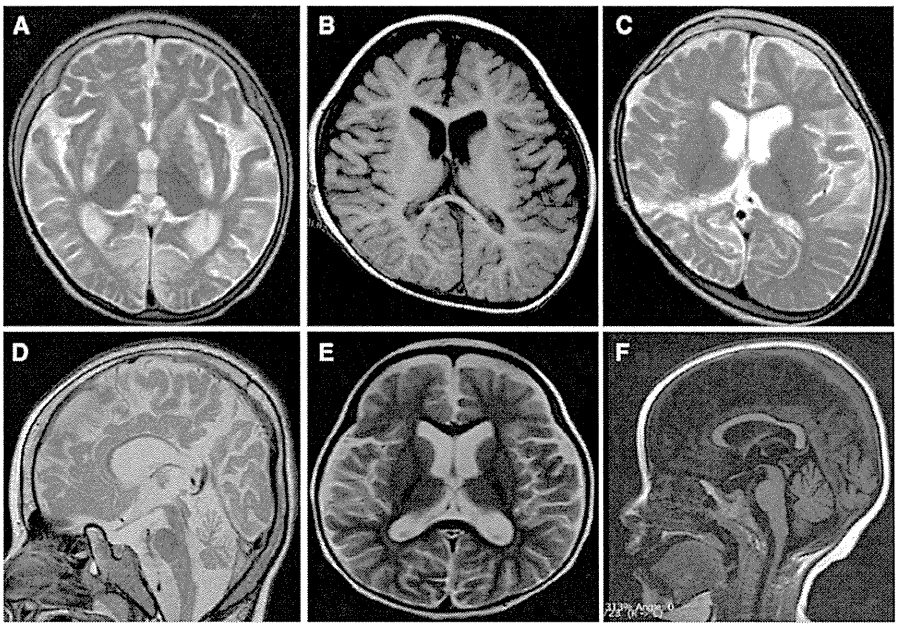

Figure 2.
Brain MRI of patients with *SCN8A* mutations. (**A**, **C**, **E**) T_2-weighted, (**B**) T_1-weighted axial images, (**D**) T_2-weighted, and (**F**) T_1-weighted sagittal images of the patients. (**A**) Patient 1 at 2 years and 11 months; (**B**) patient 2 at 1 year and 10 months; (**C**, **D**) patient 3 at 4 years; (**E**, **F**) patient 4 at 2 years. Hyperintensity in bilateral striatal bodies, and the medial occipital and temporooccipital cortexes was observed in patient 1 (**A**). Patient 2 showed mild atrophy of frontal and temporal lobes (**B**). Patient 3 showed mild brain atrophy with a dilation of the anterior horn of the lateral ventricle and a split of the right hemisphere by parieto-occipitotemporal lobotomy (**C**), as well as a thin corpus callosum and mild cerebellar atrophy (**D**). Patient 4 showed no obvious brain abnormalities (**E**, **F**).
Epilepsia © ILAE

The clinical features of patients with *SCN8A* mutations are summarized in Table 1, and their representative brain images and EEG are shown in Figures 2 and 3. All seven patients showed intractable seizures, developmental delay in infancy, or regression after seizure onset, resulting in severe intellectual disability in later life. In two patients showing developmental regression, some developmental improvements were regained with control of seizures. Four patients showed hypotonia. The onset of seizures and their types were highly variable, and included tonic–clonic seizures at the age of 3 days in patient 1 and 3 months in patient 6, atypical absence seizures at the age of 7 months

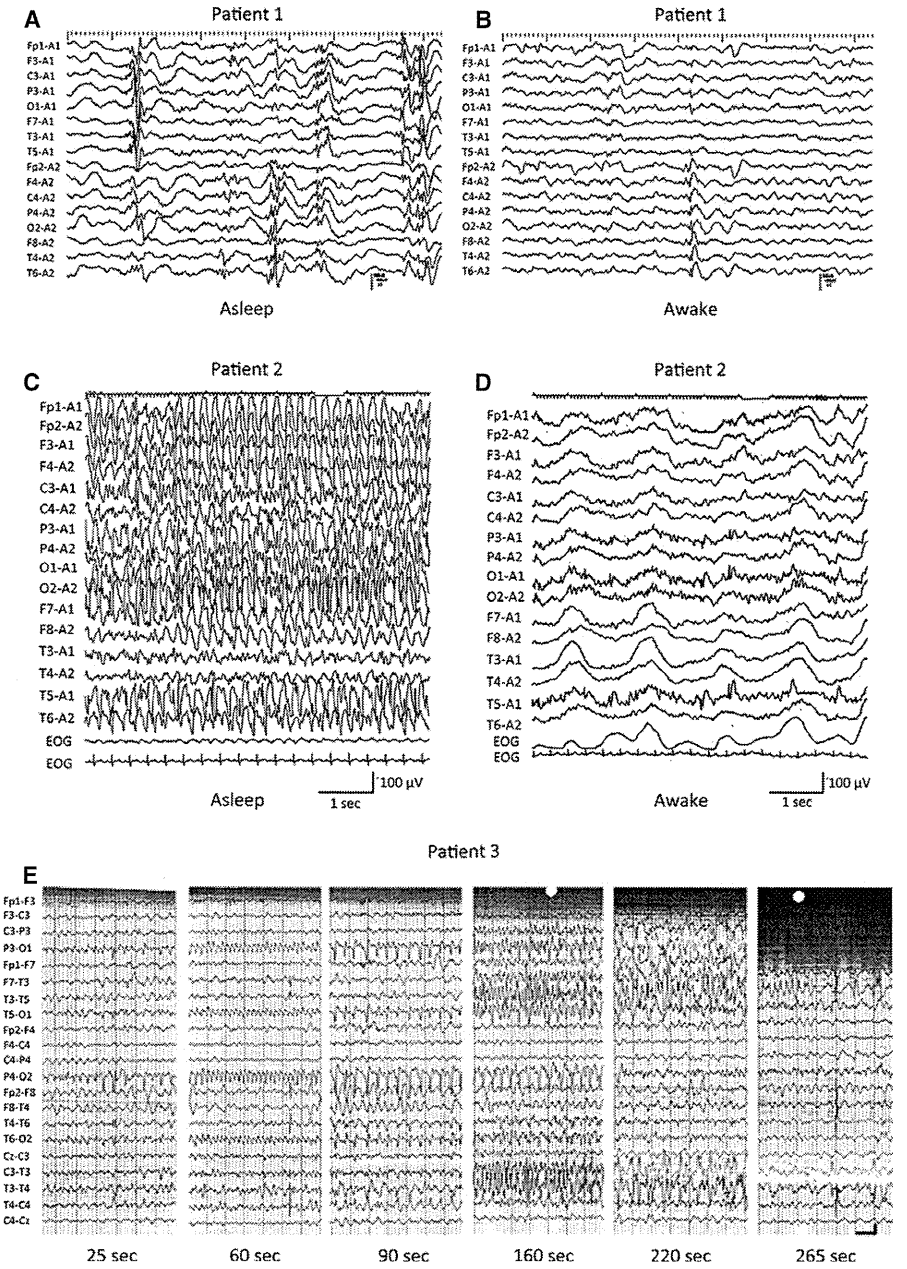

Figure 3.
EEG of patients with *SCN8A* mutations. (**A**, **B**) EEG of patient 1 at the age of 6 months. Diffuse or unilateral hemispheric irregular polyspike-and-slow wave complexes were more frequently seen when asleep (**A**) than awake (**B**). (**C**, **D**) Interictal EEG of patient 2 at the age of 5 years. Electrical status epilepticus was observed when asleep (**C**), and a left occipital predominant areal spike-and-slow wave complex occurred when awake (**D**). (**E**) Ictal EEG of patient 3 at 9 months. Left occipital sharp waves spreading to the right followed by a polyspike or fast wave at T3–T5 were seen in association with an apneic attack and right facial twitching propagating to a right hemiclonic seizure.
Epilepsia © ILAE

(patient 2), apnea attacks at 2 months (patient 3), a febrile convulsion at 3 months (patient 4), partial seizures with secondary generalization at 4 months (patient 5), and seizures manifesting as loss of tone and consciousness at 3.5 months (patient 7). Six patients developed mild cerebral atrophy, and patient 3 showed cerebellar atrophy on brain magnetic resonance imaging (MRI) (Fig. 2). The initial EEG was normal in four patients (patients 3, 4, 5, and 7). A variety of EEG abnormalities was found in patients with *SCN8A* mutations (Fig. 3). Various antiepileptic treatments were only temporarily effective in controlling seizures; however, patient 2 (now 13 years of age) has been seizure free on valproic acid since the age of 6 years, and the seizures of patients 5, 6, and 7 were almost controlled at the last examination with rare breakthrough seizures. In patients 5 and 7, carbamazepine and topiramate combination therapy was effective in controlling seizures. Ketogenic diet was effective in patient 3 who, however, demonstrated severe ileus. Phenytoin, which blocks VGSCs,[16] was used in five patients (patient 1, 2, 3, 5, and 7), showing only temporarily effects at maximum.

Discussion

It has been reported that $Na_v1.2$ (SCN2A) channels are expressed early in development, and that $Na_v1.6$ (SCN8A)