発表者名	論文タイトル名	発表誌	巻・号	ページ	出版年
Nakata T, Ito M, Azuma Y, Otsuka K, Noguchi Y, Komaki H, Okumura A, Shiraishi K, Masuda A, Natsume J, Kojima S, Ohno K.	Mutations in the C-terminal domain of ColQ in endplate acetylcholinesterase deficiency compromise ColQ-MuSK interaction.	Hum Mutat.	34	997-1004	2013
Yonekawa T, Komaki H, Saito Y, Takashima H, Sasaki M.	Congenital hypomyelinating neuropathy attributable to a de novo p.Asp61Asn mutation of the myelin protein zero gene.	Pediatr Neurol.	48	59–62	2013
Takeuchi F, Yonemoto N, Nakamura H, Shimizu R, Komaki H, Mori-Yoshimura M, Hayashi YK, Nishino I, Kawai M, Kimura E, Takeda S.	Prednisolone improves walking in Japanese Duchenne muscular dystrophy patients.	J Neurol.	In press		

発表者名	論文タイトル名	発表誌	巻・号	ページ	出版年
Kokunai Y, Nakata T, Furuta M, Sakata S, Kimura H, Aiba T, Yoshinaga M, Osaki Y, Nakamori M, Itoh H, Sato T, Kubota T, Kadota K, Shindo K, Mochizuki H, Shimizu W, Horie M, Okamura Y, Ohno K, Takahashi MP.	A Kir3.4 mutation causes Andersen–Tawil syndrome by an inhibitory effect on Kir2.1.	Neurology	印刷中		2014
Koebis M, Kiyatake T, Yamaura H, Nagano K, Higashihara M, Sonoo M, Hayashi Y, Negishi Y, Endo-Takahashi Y, Yanagihara D, Matsuda R, Takahashi MP, Nishino I, Ishiura S.	Ultrasound-enhanced delivery of Morpholino with Bubble liposomes ameliorates the myotonia of myotonic dystrophy model mice.	Sci Rep.	3	2242	2013
Oana K, Oma Y, Suo S, Takahashi MP, Nishino I, Takeda S, Ishiura S.	Manumycin A corrects aberrant splicing of Clcn1 in myotonic dystrophy type 1 (DM1) mice.	Sci Rep.	3	2142	2013
久保田智哉、高橋正紀	骨格筋チャネル病の最新知見—ミオトニー症候群と周期性四肢麻痺を中心に	医学のあゆみ	245・9	732-739	2013
高橋正紀	周期性四肢麻痺	今日の診断指針	印刷中		

発表者名	論文タイトル名	発表誌	巻・号	ページ	出版年
Ning R de Vega S, Kurihara H, Ichikawa-Tomikawa N, Xu Z,Nonaka R, Yamada Y, Miner J, Arikawa-Hirasawa E.	Laminin α1 regulates age-related mesangial cell proliferation and mesangial matrix accumulation through the TGFß pathway.	Am J Pathol	in press.		2013
Furuya N, Ikeda SI, Sato S, Soma S, Ezaki J, Trejo JA, Takeda-Ezaki M, Fujimura T, Arikawa-Hirasawa E, Tada N, Komatsu M, Tanaka K, Kominami E, Hattori N, Ueno T.	PARK2/Parkin-mediated mitochondrial clearance contributes to proteasome activation during slow-twitch muscle atrophy via NFE2L1 nuclear translocation.	Autophagy	in press.		2013
Kerever A Mercier F, Nonaka R, de Vega S, Oda Y, Zalc B, Okada Y, Hattori N, Yamada Y, Arikawa-Hirasawa,	Perlecan is required for FGF-2 signaling in the neural stem cell niche.	Stem Cell Res	121	492-505.	2013

発表者名	論文タイトル名	発表誌	巻・号	ページ	出版年
Douet V, Arikawa-Hirasawa E, Mercier F	Fractone-heparan sulfates mediate FGF-2 stimulation of cell proliferation in the adult subventricular zone	Cell Prolif	46	137-145.	2013
Nakata T, Ito M, Azuma Y, Otsuka K, Noguchi Y, Komaki H, Okumura A, Shiraishi K, Masuda A, Natsume J, Kojima S, Ohno K.	Mutations in the C-terminal domain of ColQ in endplate acetylcholinesterase deficiency compromise ColQ-MuSK interaction	Hum Mutat	34	997-1004	2013
Selcen D, Shen XM, Milone M, Brengman J, Ohno K, Deymeer F, Finkel R, Rowin J, Engel AG.	Gfpt1-myasthenia: Clinical, structural, and electrophysiologic heterogeneity	Neurology	81	370-378	2013
Fujioka Y, Ishigaki S, Masuda A, Iguchi Y, Udagawa T, Watanabe H, Katsuno M, Ohno K, Sobue G.	FUS-regulated region- and cell-type-specific transcriptome is associated with cell selectivity in ALS/FTLD	Sci Rep	3	2388	2013

発表者名	論文タイトル名	発表誌	巻・号	ページ	出版年
Rahman MA, Masuda A, Ohe K, Ito M, Hutchinson DO, Mayeda A, Engel AG, Ohno K.	HnRNP L and hnRNP LL antagonistically modulate PTB-mediated splicing suppression of CHRNA1 pre-mRNA	Sci Rep	3	2931	2013
Ohno K, Ito M, Kawakami Y, Krejci E, Engel AG.	Specific binding of collagen Q to the neuromuscular junction is exploited to cure congenital myasthenia and to explore bases of myasthenia gravis	Chem Biol Interact	203	pp 335-340 (査読有)	2013
Ohno K, Ito M, Kawakami Y.	Collagen Q is a key player for developing rational therapy for congenital myasthenia and for dissecting the mechanisms of anti-MuSK myasthenia gravis	J Mol Neurosci, Springer, New York		DOI 10.1007 /s12031 -013-01 70-x, 3 pages (査読有)	2013
Ohkawara B, Cabrera Serrano M, Nakata T, Milone M, Asai N, Ito K, Ito M, Masuda A, Ito Y, Engel AG, Ohno K.	LRP4 third ß-propeller domain mutations cause novel congenital myasthenia by compromising agrin-mediated MuSK signaling in a position-specific manner	Hum Mol Genet		in press	
Ohno K, Ohkawara B, Ito M, Engel AG.	Molecular Genetics of Congenital Myasthenic Syndromes	eLS. John Wiley & Sons, Inc.		in press (査読有)	

発表者名	論文タイトル名	発表誌	巻・号	ページ	出版年
Sato T, Hayashi YK, Oya Y, Kondo T, Sugie K, Kaneda D, Houzen H, Yabe I, Sasaki H, Noguchi S, Nonaka I, Osawa M, Nishino I.	DNAJB6 myopathy in an Asian cohort and cytoplasmic/nuclear inclusions.	Neuromuscul Disord.	23(3)	269-276	2013
Kataoka H, Saeki K, Kobayashi Y, Kiriyama T, Sugie K, Ueno S.	Predictors of outcomes in acyclovir-treated limbic encephalitis.	J Infect	66(2)	201-205	2013
杉江和馬.	ライソゾーム膜の異常：ダノン病. 神経症候群 III（第 2 版）－その他の神経疾患を含めて－.	別冊日本臨床　新領域別症候群シリーズ	28	印刷中	2014
Yamashita S, Kimura E, Tawara N, et al.	Optineurin is potentially associated with TDP-43 and involved in the pathogenesis of inclusion body myositis.	Neuropathol Appl Neurobiol.	39 (4)	406-416	2013
Uchino M, Yamashita S, Uchino K, et al.	Muscle biopsy findings predictive of malignancy in rare infiltrative dermatomyositis.	Clin Neurol Neurosurg.	115 (5)	603-606	2013
Tanaka A, Woltjen K, Miyake K, et al.	Efficient and Reproducible Myogenic Differentiation from Human iPS Cells: Prospects for Modeling Miyoshi Myopathy In Vitro.	PLoS One	8 (4)	e61540	2013

発表者名	論文タイトル名	発表誌	巻・号	ページ	出版年
Mori-Yoshimura M, Momma K, Suzuki N, et al.	Heterozygous UDP-GlcNAc 2-epimerase and N-acetylmannosamine kinase domain mutations in the GNE gene result in a less severe GNE myopathy phenotype compared to homozygous N-acetylmannosamine kinase domain mutations	Journal of the Neurological Sciences	318(1-2)	100-105	2012
Nakamura S, Kaneko S, Shinde A, Morita J, Fujita K, Nakano S, Kusaka H.	Prednisolone-sparing effect of cyclosporin A therapy for very elderly patients with myasthenia gravis.	Neuromuscul Disord.	23(2)	176-179	2013
Nakamura M, Kaneko S, Ito H, Jiang S, Fujita K, Wate R, Nakano S, Fujisawa J, Kusaka H.	Activation of transforming growth factor-ß/Smad signaling reduces aggregate formation of mislocalized TAR DNA-binding protein-43. ;:	Neurodegener Dis.	11(4)	182-193.	2013
中野　智	先天性ミオトニー	今日の神経疾患治療指針　第2版 水澤英洋、鈴木側宏、梶龍兒　他編集	医学書院、東京	786-788,	2013

発表者名	論文タイトル名	発表誌	巻・号	ページ	出版年
中野　智	11. 筋疾患	わかりやすい内科学 第4版　井村裕夫　他編集	文光堂、東京	646-653	2014
Rumiko Izumi, Tetsuya Niihori, Yoko Aoki1, Naoki Suzuki, Masaaki Kato, Hitoshi Warita, Toshiaki Takahashi, Maki Tateyama, Takeshi Nagashima, Ryo Funayama, Koji Abe, Keiko Nakayama, Masashi Aoki and Yoichi Matsubara	Exome sequencing identifies a novel TTN mutation in a family with hereditary myopathy with early respiratory failure	Journal of Human Genetics		1-8	2013
Mori-Yoshimura M, Oya Y, Hayashi YK, Noguchi S, Nishino I, Murata M	Respiratory dysfunction in patients severely affected by GNE myopathy (distal myopathy with rimmed vacuoles).	Neuromuscul Disord.	23(1)	84-88	2013
Ken-ya Murata, Ken Kouda, Fumihiro Tajima, Tomoyoshi Kondo	Balloon Dilation in Sporadic Inclusion Body Myositis Pstients with Dysphagia	Clinical Medicine Insights		1-7	2013
Yamashita S, Kimura E, Tawara N, et al.	Optineurin is potentially associated with TDP-43 and involved in the pathogenesis of inclusion body myositis.	Neuropathol Appl Neurobiol.		In press	2013

発表者名	論文タイトル名	発表誌	巻・号	ページ	出版年
Uchino M, Yamashita S, Uchino K, et al.	Muscle biopsy findings predictive of malignancy in rare infiltrative dermatomyositis.	Clin Neurol Neurosurg.		In press	2013
Ramachandran N, Munteanu I, Wang P, Ruggieri A, Rilstone JJ, Israelian N, Naranian T, Paroutis P,Guo R, Ren ZP, Nishino I, Chabrol B, Pellissier JF, Minetti C, Udd B, Fardeau M, Tailor CS,Mahuran DJ, Kissel JT, Kalimo H,Levy N, Manolson MF, Ackerley CA, Minassian BA	VMA21 deficiency Prevents vacuolar ATPase assembly and Causes autophagic vacuolar myopathy.	Acta Neuropathol.	Epub ahead of print		
Furuta A, Wakabayashi K, Haratake J, Kikuchi H, Kabuta T, Mori F, Tokonami F, Katsumi Y, Tanioka F, Uchiyama Y, Nishino I, Wada K	Lysosomal storage and advanced senescence in the brain of LAMP-2 deficient Danon Disease.	Acta Neuropathol.	Epub ahead of print		

発表者名	論文タイトル名	発表誌	巻・号	ページ	出版年
Neumann M, Valori CF, Ansorge O, Kretzschmar HA, Munoz DG, Kusaka H, Yokota O, Ishihara K, Ang LC, Bilbao JM, Mackenzie IR.	Transportin 1 accumulates specifically with FET proteins but no other transportin cargos in FTLD-FUS and is absent in FUS inclusions in ALS with FUS mutations.	Acta neuropathologica	124(5)	705-716	2012
Nakamura S, Nakano S, Nishii M, Kaneko S, Kusaka H.	Localization of O-GlcNAc-modified proteins in neuromuscular diseases.	Medical molecular morphology	45(2)	86-90	2012
中野　智，日下博文	「封入体筋炎における核遺残物を含んだ空胞」 特集　細胞の分子構造と機能—核以外の細胞小器官 8. 膜小胞と封入体	生体の科学	63:534-535		2012
Inamori Y, Higuchi I, Inoue T, Sakiyama Y, Hashiguchi A, Higashi K, Shiraishi T, Okubo R, Arimura K, Mitsuyama Y, Takashima H.	Inclusion body myositis coexisting with hypertrophic cardiomyopathy: an autopsy study.	Neuromuscular Disorders	22	747-754	2012
Uchino M, Yamashita S, Uchino K, et al.	Long-term outcome of polymyositis treated with high single-dose alternate-day prednisolone therapy.	Eur Neurol.	68(2)	117-21	2012
高松直子、寺澤由佳、酒井和香、宮本亮介、宮城愛、島谷佳光、佐藤健太、松井尚子、和泉唯信、梶龍兒	筋超音波所見を契機として確定診断できたサルコイドーシスの一例	Neurosonology	25(1)	13-16	2012

発表者名	論文タイトル名	発表誌	巻・号	ページ	出版年
Keduka E, Hayashi YK, Shalaby S, Mitsuhashi H, Noguchi S, Nonaka I, Nishino I	*In Vivo* Characterization of Mutant Myotilins.	Am J Pathol.	180・4	1570-1580	2012
Tsuburaya RS, Monma K, Oya Y, Nakayama T, Fukuda T, Sugie H, Hayashi YK, Nonaka I, Nishino I	Acid phosphatase-positive globular inclusions is a good diagnostic marker for two patients with adult-onset Pompe disease lacking disease specific pathology.	Neuromuscul Disord.	22・5	389-393	2012
Suzuki S, Hayashi YK, Kuwana M, Tsuburaya R, Suzuki N, Nishino I	Myopathy associated with antibodies to signal recognition particle: disease progression and neurological outcome.	Arch Neurol.	69・6	728-732	2012
Yoshinaga Y. Sakoda S-I,Good JM, Takahashi MP, Kubota T, Arikawa-Hirasawa E, Nakata T, Ohno K, Kitamura T, Kobayashi K, Ohtsuka Y.	A novel mutation in SCN4A causes severe myotonia and school-age-onset paralytic episodes.	J Neurol Sci.	315・1-2	15-19	2012
Kokunai Y, Goto K, Kubota T, Fukuoka T, Sakoda S, Ibi T, Doyu M, Mochizuki H, Sahashi K, Takahashi MP.	A sodium channel myotonia due to a novel SCN4A mutation accompanied by acquired autoimmune myasthenia gravis.	Neurosci Lett.	519・1	67-72	2012

発表者名	論文タイトル名	発表誌	巻・号	ページ	出版年
Muneaki Ishijima , Nobuharu Suzuki, Kentaro Hozumi, Tomoya Matsunobu, Keisuke Kosaki , Haruka Kaneko, JohnR. Hassell,Eri Arikawa-Hirasawa , Yoshihiko Yamada ,	Perlecan modulates VEGF signaling and is essential for vascularization in endochondral bone formation	Matrix Biology	12138	In Press (1-5)	2012
Harumi Yoshinaga , Shunichi Sakoda, Jean-Marc Good, Masanori P. Takahashi , Tomoya Kubota , Eri Arikawa-Hirasawa , Tomohiko Nakata, Kinji Ohno , Tetsuro Kitamura, Katsuhiro Kobayashi, Yoko Ohtsuka	A novel mutation in SCN4A causes severe myotonia and school-age-onset paralytic episodes	Journal of the Neurological Sciences	12138	In Press (1-5)	2012

発表者名	論文タイトル名	発表誌	巻・号	ページ	出版年
Takenori Inomata, Nobuyuki, Ebihara, Toshinari Funaki, Akira Matsuda, Yasuo Watanabe, Liang Ning, Zhuo Xu, Akira Murakami, and Eri Arikawa-Hirasawa,	Perlecan-Deficient Mutation Impairs Corneal Epithelial Structure	IOVS	Vol.53, No. 3	1277-1284	2012
Masuda A, Andersen HS, Doktor TK, Okamoto T, Ito M, Andresen BS, Ohno K.	CUGBP1 and MBNL1 preferentially bind to 3' UTRs and facilitate mRNA decay	*Sci Rep*	2	209	2012
Ito M, Suzuki Y, Okada T, Fukudome T, Yoshimura T, Masuda A, Takeda S, Krejci E, Ohno K.	Protein-anchoring strategy for delivering acetylcholinesterase to the neuromuscular junction	*Mol Ther*	20	1384-1392	2012
Ishigaki S, Masuda A, Fujioka Y, Iguchi Y, Katsuno M, Shibata A, Urano F, Sobue G, Ohno K.	Position-dependent fus-rna interactions regulate alternative splicing events and transcriptions	*Sci Rep*	2	529	2012
Sugie K, Hayashi YK, Goto K, Nishino I, Ueno S.	Unusual presentation: Unilateral arm and contralateral leg amyotrophy in FSHD.	Neurology	79(5)	e46	2012

発表者名	論文タイトル名	発表誌	巻・号	ページ	出版年
Sugie K, Tonomura Y, Ueno S.	Characterization of dermatomyositis with coexistence of anti-Jo-1 and anti-SRP antibodies.	Intern Med	51(7)	799-802	2012
杉江和馬.	ライソゾーム病：ダノン病. 先天代謝異常症候群－病因・病態研究、診断・治療の進歩－.	日本臨床	20	588-592	2012
Momma K, Noguchi S, Malicdan MC, Hayashi YK, Minami N, Kamakura K, Nonaka I, Nishino I	Rimmed vacuoles in Becker muscular dystrophy have similar features with inclusion myopathies.	PLoS One.	7(12)	e52002	2012
Komagamine T, Kawai M, Kokubun N, Miyatake S, Ogata K, Hayashi YK, Nishino I, Hirata K	Selective muscle involvement in a family affected by a second LIM domain mutation of fhl1: An imaging study using computed tomography.	J Neurol Sci.	318(2012)	163-167	2012
Mori-Yoshimura M, Monma K, Suzuki N, Aoki M, Kumamoto T, Tanaka K, Tomimitsu H, Nakano S, Sonoo M, Shimizu J, Sugie K, Nakamura H, Oya Y, Hayashi YK, Malicdan MC, Noguchi S, Murata M, Nishino I	Heterozygous UDP-GlcNAc 2-epimerase and N-acetylmannosamine kinase domain mutations in the GNE gene result in a less severe GNE myopathy phenotype compared to homozygous N-acetylmannosamine kinase domain mutations.	J Neurol Sci.	318(2012):	100-105	2012

発表者名	論文タイトル名	発表誌	巻・号	ページ	出版年
Nakamura M, Kaneko S, Ito H, Jiang S, Fujita K, Wate R, Nakano S, Fujisawa JI, Kusaka H.	Activation of Transforming Growth Factor-ß/Smad Signaling Reduces Aggregate Formation of Mislocalized TAR DNA-Binding Protein-43.	Neuro-degenerative diseases	:Jul 10. [Epub ahead of print]		2012
Nakamura S, Kaneko S, Shinde A, Morita JI, Fujita K, Nakano S, Kusaka H.	Prednisolone-sparing effect of cyclosporin A therapy for very elderly patients with myasthenia gravis.	Neuromuscular disorders : NMD	:Dec 10. [Epub ahead of print]		2012
Nakamura M, Kaneko S, Wate R, Asayama S, Nakamura Y, Fujita K, Ito H, Kusaka H.	Regionally different immunoreactivity for Smurf2 and pSmad2/3 in TDP-43-positive inclusions of amyotrophic lateral sclerosis.	Neuropathology and applied neurobiology	:Mar 21. [Epub ahead of print]		2012
Yamashita S, Mori A, Sakaguchi H, et al.	Sporadic juvenile amyotrophic lateral sclerosis caused by mutant FUS/TLS: possible association of mental retardation with this mutation.	J Neurol.	259(6)	1039-44	2012
Yamashita S, Sakaguchi H, Mori A, et al.	Significant CMAP decrement by repetitive nerve stimulation is more frequent in median than ulnar nerves of patients with amyotrophic lateral sclerosis.	Muscle Nerve	45(3)	426-8	2012
小牧宏文	小児の診療手技 100 筋生検	小児科診療	75	276-278	2012

発表者名	論文タイトル名	発表誌	巻・号	ページ	出版年
小牧宏文	症候・疾患と検査・診断　神経筋疾患の診断	小児神経学の進歩	41	69-77	2012
石山昭彦, 小牧宏文	小児慢性疾患の生活指導－最新の知見から－　10.神経・筋疾患　2) 先天性ミオパチー	小児科臨床	65巻4号	839-846	2012
石山昭彦, 藤義朗	先天性筋ジストロフィー	小児内科	44　巻増刊号	794-795	2012
佐々木良元、高橋正紀、穀内洋介、平山正昭、衣斐　達、冨本秀和、望月秀樹、佐橋　功	骨格筋型塩化物イオンチャネル遺伝子（CLCN1）の複合ヘテロ接合体変異で重症化したThomsen病	臨床神経学	印刷中		
Yoshinaga H, Sakoda S, Good J M, Takahashi M P, Kubota T, Arikawa-Hirasawa E, Nakata T, Ohno K, Kitamura T, Kobayashi K, Ohtsuka Y.	A novel mutation in *SCN4A* causes severe myotonia and school-age-onset paralytic episodes	*J Neurol Sci*	315	15-19	2012
Matsuura T, Minami N, Arahata H, Ohno K, Abe K, Hayashi YK, Nishino I.	Myotonic dystrophy type 2 is rare in the Japanese population	*J Hum Genet*	57	219-220	2012

発表者名	論文タイトル名	発表誌	巻・号	ページ	出版年
Yamashita Y*, Matsuura T*, Shinmi J, Amakusa Y, Masuda A, Ito M, Kinoshita M, Furuya H, Abe K, Ibi T, Sahashi K, Ohno K.	Four parameters increase the sensitivity and specificity of the exon array analysis and disclose twenty-five novel aberrantly spliced exons in myotonic dystrophy	*J Hum Genet*	57	368-374	2012
Yamamoto R, Matsushita M, Kitoh H, Masuda A, Ito M, Katagiri T, Kawai T, Ishiguro N, Ohno K.	Clinically applicable antianginal agents suppress osteoblastic transformation of myogenic cells and heterotopic ossifications in mice	*J Bone Miner Metab*	31	26-33	2012
Ohe K, Masuda A, Ohno K.	Intronic and exonic nucleotide variations that affect rna splicing in humans	*Introduction to Sequence and Genome Analysis.* iConcept Press, Hong Kong		in press	2012

発表者名	論文タイトル名	発表誌	巻・号	ページ	出版年
Mori-Yoshimura M, Monma K,Suzuki N, Aoki M, Kumamoto T, Tanaka K, Tomimitsu H, Nakano S, Sonoo M, Shimizu J,Sugie K, Nakamura H, Oya Y, Hayashi YK, Malicdan MC, Noguchi S, Murata M, Nishino I.	Heterozygous UDP-GlcNAc 2-epimerase and N-acetylmannosamine kinase domain mutations in the GNE gene result in a less severe GNE myopathy phenotype compared to homozygous N-acetylmannosamine kinase domain mutations.	J Neurol Sci	318(1-2)	100-105	2012
Sawa N, Kataoka H, Sugie K, Kawahara M, Horikawa H, Kusunoki S, Ueno S.	Clinical analysis and outcomes of amyotrophic lateral sclerosis with demyelinating polyneuropathy.	Amyotroph Lateral Scler	13(1)	125-31	2012
杉江和馬.	顔面肩甲上腕型筋ジストロフィーの骨格筋障害の分布.	難病と在宅ケア	17(10)	53-55	2012

Ⅳ. 研究成果に関する刊行物

JNNP Online First, published on September 11, 2013 as 10.1136/jnnp-2013-305587

RESEARCH PAPER

Mutation profile of the *GNE* gene in Japanese patients with distal myopathy with rimmed vacuoles (GNE myopathy)

Anna Cho,[1] Yukiko K Hayashi,[1,2,3] Kazunari Monma,[1] Yasushi Oya,[4] Satoru Noguchi,[1] Ikuya Nonaka,[1] Ichizo Nishino[1,2]

▸ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/jnnp-2013-305587).

[1]Department of Neuromuscular Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Tokyo, Japan
[2]Department of Clinical Development, Translational Medical Center, National Center of Neurology and Psychiatry, Tokyo, Japan
[3]Department of Neurophysiology, Tokyo Medical University, Tokyo, Japan
[4]Department of Neurology, National Center Hospital, National Center of Neurology and Psychiatry, Tokyo, Japan

Correspondence to
Professor Yukiko K Hayashi, Department of Neurophysiology, Tokyo Medical University, 6-1-1 Shinjuku, Shinjuku, Tokyo 160-8402, Japan; yhayashi@tokyo-med.ac.jp

Received 4 June 2013
Revised 21 August 2013
Accepted 22 August 2013

To cite: Cho A, Hayashi YK, Monma K, *et al*. *J Neurol Neurosurg Psychiatry* Published Online First: [*please include* Day Month Year] doi:10.1136/jnnp-2013-305587

ABSTRACT

Background GNE myopathy (also called distal myopathy with rimmed vacuoles or hereditary inclusion body myopathy) is an autosomal recessive myopathy characterised by skeletal muscle atrophy and weakness that preferentially involve the distal muscles. It is caused by mutations in the gene encoding a key enzyme in sialic acid biosynthesis, UDP-*N*-acetylglucosamine 2-epimerase/*N*-acetylmannosamine kinase (GNE).

Methods We analysed the *GNE* gene in 212 Japanese GNE myopathy patients. A retrospective medical record review was carried out to explore genotype–phenotype correlation.

Results Sixty-three different mutations including 25 novel mutations were identified: 50 missense mutations, 2 nonsense mutations, 1 insertion, 4 deletions, 5 intronic mutations and 1 single exon deletion. The most frequent mutation in the Japanese population is c.1714G>C (p.Val572Leu), which accounts for 48.3% of total alleles. Homozygosity for this mutation results in more severe phenotypes with earlier onset and faster progression of the disease. In contrast, the second most common mutation, c.527A>T (p.Asp176Val), seems to be a mild mutation as the onset of the disease is much later in the compound heterozygotes with this mutation and c.1714G>C than the patients homozygous for c.1714G>C. Although the allele frequency is 22.4%, there are only three homozygotes for c.527A>T, raising a possibility that a significant number of c.527A>T homozygotes may not develop an apparent disease.

Conclusions Here, we report the mutation profile of the *GNE* gene in 212 Japanese GNE myopathy patients, which is the largest single-ethnic cohort for this ultra-orphan disease. We confirmed the clinical difference between mutation groups. However, we should note that the statistical summary cannot predict clinical course of every patient.

INTRODUCTION

GNE myopathy, which is also known as distal myopathy with rimmed vacuoles,[1] quadriceps sparing myopathy[2] or hereditary inclusion body myopathy (hIBM),[3] is an autosomal recessive myopathy characterised by skeletal muscle atrophy and weakness that preferentially involve the distal muscles such as the tibialis anterior. It is a progressive disease, whereby the symptoms of muscle weakness start to affect the patient from the second or third decade of life, and most of the patients become wheelchair-bound between twenties and sixties.[4] The characteristic histopathological features in muscle biopsy include muscle fibre atrophy with the presence of rimmed vacuoles and intracellular congophilic deposits.[4 5] GNE myopathy is caused by mutations in the gene encoding a key enzyme in sialic acid biosynthesis, UDP-*N*-acetylglucosamine 2-epimerase/*N*-acetylmannosamine kinase (GNE).[6–8] Genetically confirmed GNE myopathy was initially recognised in Iranian Jews and Japanese,[7 9] but later appeared to be widely distributed throughout the world. More than 100 mutations in the *GNE* gene have been described up to date.

During the last decade, there has been extensive experimental work to elucidate the pathogenesis and to develop therapeutic strategies of GNE myopathy.[6 10–12] Better knowledge on the basis of those research achievements have currently enabled us to enter the era of clinical trial for human patients. At this moment, the identification of new GNE myopathy patients with precise genetic diagnosis and the expansion of global spectrum of *GNE* mutations are timely and important. Here, we report the molecular profile of Japanese GNE myopathy patients with a brief discussion of genotype–phenotype correlations.

METHODS

Patients

Two hundred and twelve patients from 201 unrelated Japanese families were included in this study. There were 117 female and 95 male patients. All cases were genetically confirmed as GNE myopathy. A retrospective medical record review was carried out to explore genotype–phenotype correlation. Informed consent was obtained for the collection of clinical data and extraction of DNA to perform mutation analysis.

Genetic analysis

DNA was extracted from peripheral blood leukocytes or skeletal muscle tissue. We used the previously described sequencing method to describe mutations at cDNA level.[7] All exons and splice regions of the *GNE* gene were sequenced. NM_005476.5 was used as a reference sequence. We screened 100 alleles from normal Japanese individuals to determine the significance of novel variations.

Pathological analysis

To evaluate histopathological phenotype according to genotype, we analysed muscle biopsies from two