厚生労働科学研究費補助金（創薬基盤推進研究事業　ヒトゲノムテーラーメード研究）
（総合）分担研究報告書

ゲノム解析によるパーキンソン病遺伝子同定と創薬・テーラーメード研究

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研究要旨

パーキンソン病治療薬であるドパミンアゴニストの副作用との関連を中心に検討した。麦角系ドパミンアゴニストでは用量依存性に心臓弁膜症の頻度が増加したが SNP 解析をすることに事前に副作用を予知できる可能性が有ると思われた。症例を集積したので今後 SNP 解析を進めていく予定である。

A.研究目的

パーキンソン病治療薬であるドパミンアゴニストの副作用との関連をより安全なパーキンソン病治療が可能とするために検討した。

B.研究方法

パーキンソン病当初210例で患者背景等の調査と心臓弁膜症検査のための心エコー検査を実施し、追跡フォロー中である。その後 50 例の症例追加を行った。

(倫理面への配慮)

DNA は文書同意、心エコーは口頭同意を得て実施。IRB 承認すみ。

C.研究結果

1)DNA 解析は症例不充分で行っていない。

2)心エコーでは麦角系ドパミンアゴニストで用量依存性に心臓弁膜症の増加を確認した。

D.考察

心エコーでは麦角系ドパミンアゴニストで用量依存性に心臓弁膜症の増加を確認したことは新知見でありドパミンアゴニストの安全な使用に寄与すると考える。

SNP 解析により心臓弁膜症発現の可能性を予測できればより安全なパーキンソン病治療が可能となる。

E.結論

麦角系ドパミンアゴニストで用量依存性に心臓弁膜症の増加があり、高用量の使用は危険があるので注意を要する。

F.健康危険情報

麦角系ドパミンアゴニストで用量依存性に心臓弁膜症の増加することへの注意喚起

G.研究発表

1.　論文発表
（発表誌名巻号・頁・発行年等も記入）

1. Satake W, Nakabayashi Y, Mizuta I, Hirota Y, Ito C, Kubo M, Kawaguchi T, Tsunoda T, Watanabe M, Takeda A, Tomiyama H, Nakashima K, Hasegawa K,

Obata F, Yoshikawa T, Kawakami H, Sakoda S, Yamamoto M, Hattori N, Murata M, Nakamura Y, Toda T. Genome-wide association study identifies common variants at four loci as genetic risk factors for Parkinson's disease.
Nat Genet. 2009 Dec;41(12):1303-7.

2. Antonini A, Tolosa E, Mizuno Y, Yamamoto M, Poewe WH. A reassessment of risks and benefits of dopamine agonists in Parkinson's disease.
Lancet Neurol. 2009 Oct;8(10):929-37.

3. Mitsui J, Mizuta I, Toyoda A, Ashida R, Takahashi Y, Goto J, Fukuda Y, Date H, Iwata A, Yamamoto M, Hattori N, Murata M, Toda T, Tsuji S. Mutations for Gaucher disease confer high susceptibility to Parkinson disease. Arch Neurol. 2009 May;66(5):571-6.

4. Zabetian CP, Yamamoto M, Lopez AN, Ujike H, Mata IF, Izumi Y, Kaji R, Maruyama H, Morino H, Oda M, Hutter CM, Edwards KL, Schellenberg GD, Tsuang DW, Yearout D, Larson EB, Kawakami H. LRRK2 mutations and risk variants in Japanese patients with Parkinson's disease. Mov Disord. 2009 May 15;24(7):1034-41.

2. 学会発表
山本光利　パーキンソン病：早期治療　第3回パーキンソン病・運動障害疾患コングレス
2009年10月8日　京都

H.知的財産権の出願・登録状況
（予定を含む。）
1. 特許取得

なし
2. 実用新案登録

なし

3.その他
なし

III. 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
服部信孝他		水野 美邦 編著	ＥＢＭのコンセプトを取り入れたパーキンソン病ハンドブック　改訂２版	中外医学社	東京	2007	282-384
Kanagawa M, Toda T	Fukutin and Fukuyama congenital muscular dystrophy.	Taniguchi. N, et.al. eds	Glycoscience Lab Manual	Elsevier Japan	Japan	2008	309-312
村田美穂	進行性核上性麻痺	小林祥泰・水沢英洋	神経疾患最新の治療	南江堂	東京	2009	188-189
村田美穂	やさしいパーキンソン病の自己管理	村田美穂	やさしいパーキンソン病の自己管理	医薬ジャーナル社	大阪	2009	
村田美穂	Q58ゾニサミドはどのような場合に使用するのがよいか、また、なぜ効くのか、その使い方も説明してください。	水野美邦	パーキンソン病診療Ｑ＆Ａ	中外医学社	東京	2009	176-177
村田美穂	パーキンソン病におけるレボドパ治療の位置づけは？	服部信孝	いきなり名医 パーキンソン病Ｑ＆Ａ	日本医事新報社	東京	2009	47-49

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
Satake W, Mizuta I, Suzuki S, Nakabayashi Y, Ito C, Watanabe M, Takeda A, Hasegawa K, Sakoda S, Yamamoto M, Hattori N, Murata M, Toda T	Fibroblast growth factor 20 gene and Parkinson's disease in the Japanese population	Neuroreport	18	937-940	2007
Nagai Y, Inui T, Popiel HA, Fujikake N, Hasegawa K, Urade Y, Goto Y, Naiki H, Toda T	A toxic monomeric conformer of the polyglutamine protein	Nature Struct Mol Biol	14	332-340	2007
Kano H, Kurahashi H, Toda T	Genetically regulated epigenetic transcriptional activation of retrotransposon insertion confers mouse dactylaplasia phenotype	Proc Natl Acad Sci USA	104	19034-19039	2007
Funayama M, Li Y, Tomiyama H, Yoshino H, Imamichi Y, Yamamoto M, Murata M, Toda T, Mizuno Y, Hattori N	Leucine-Rich Repeat kinase 2 G2385R variant is a risk factor for Parkinson disease in Asian population	Neuroreport	18	273-275	2007
Saito F, Masaki T, Saito Y, Nakamura A, Takeda S, Shimizu T, Toda T, Matsumura K	Defective peripheral nerve myelination and neuromuscular junction formation in fukutin-deficient chimeric mouse	J Neurochem	101	1712-1722	2007
Popiel HA, Nagai Y, Fujikake N, Toda T	Protein transduction domain-mediated delivery of QBP1 suppresses polyglutamine-induced neurodegeneration in vivo	Mol Ther	15	303-309	2007
Chiyonobu T, Hayashi S, Kobayashi K, Morimoto M, Miyanomae Y, Nishimura A, Nishimoto A, Ito C, Imoto I, Sugimoto T, Jia Z, Inazawa J, Toda T	Partial tandem duplication of GRIA3 in a male with mental retardation	Am J Med Genet	143	1448-1455	2007

Amino T, Ishikawa K, Toru S, Ishiguro T, Sato N, Tsunemi T, Murata M, Kobayashi K, Inazawa J, Toda T, Mizusawa H	Redefining the disease locus of 16q22.1-linked autosomal dominant cerebellar ataxia	J Hum Genet	52	643-649	2007
Takahashi Y, Okamoto Y, Popiel HA, Fujikake N, Toda T, Kinjo M, Nagai Y	Detection of polyglutamine protein oligomers in cells by fluorescence correlation spectroscopy	J Biol Chem	282	24039-24048	2007
Tagawa K, Marubuchi S, Qi ML, Enokido Y, Tamura T, Inagaki R, Murata M, Kanazawa I, Wanker EE, Okazawa H	The induction levels of heat shock protein 70 differentiate the vulnerabilities to mutant huntingtin among neuronal subtypes	J Neurosci	27	868-880	2007
Ishihara L, Gibson RA, Warren L, Amouri R, Lyons K, Wielinski C, Hunter C, Swartz JE, Elango R, Akkari PA, Leppert D, Surh L, Reeves KH, Thomas S, Ragone L, Hattori N, Pahwa R, Jankovic J, Nance M, Freeman A, Gouider-Khouja N, Kefi M, Zouari M, Ben Sassi S, Ben Yahmed S, El Euch-Fayeche G, Middleton L, Burn DJ, Watts RL, Hentati F	Screening for Lrrk2 G2019S and clinical comparison of Tunisian and North American Caucasian Parkinson's disease families	Mov Disord	22	55-61	2007
Ihara M, Yamasaki N, Hagiwara A, Tanigaki A, Kitano A, Hikawa R, Tomimoto H, Noda M, Takanashi M, Mori H, Hattori N, Miyakawa T, Kinoshita M	Sept4, a Component of Presynaptic Scaffold and Lewy Bodies, Is Required for the Suppression of alpha-Synuclein Neurotoxicity	Neuron	53	519-33	2007

Ephraty L, Porat O, Israeli D, Cohen OS, Tunkel O, Yael S, Hatano Y, Hattori N, Hassin-Baer S	Neuropsychiatric and cognitive features in autosomal-recessive early parkinsonism due to PINK1 mutations	Mov Disord	22	566-569	2007
Kono S, Shirakawa K, Ouchi Y, Sakamoto M, Ida H, Sugiura T, Tomiyama, H, Suzuki H, Takahashi Y, Miyajima H, Hattori N, Mizuno Y	Dopaminergic neuronal dysfunction associated with parkinsonism in both a Gaucher disease patient and a carrier	J Neurol Sci	252	181-184	2007
Hatano T, Kubo S, Imai S, Maeda M, Ishikawa K, Mizuno Y, Hattori N	Leucine-rich repeat kinase 2 associates with lipid rafts	Hum Mol Genet	16	678-690	2007
Yoshioka M, Higuchi Y, Fujii T, Aiba H, Toda T	Seizure-genotype relationship in Fukuyama-type congenital muscular dystrophy	Brain Dev	30	59-67	2008
Kumazawa R, Tomiyama H, Li Y, Imamichi Y, Funayama M, Yoshino H, Yokochi F, Fukusako T, Takehisa Y, Kashihara K, Kondo T, Elibol B, Bostantjopoulou S, Toda T, Takahashi H, Yoshii F, Mizuno Y, Hattori N	Mutation analysis of the PINK1 gene in 391 patients with Parkinson's disease	Arch Neurol	65	802-808	2008
Mizuta I, Tsunoda T, Satake W, Nakabayashi Y, Watanabe M, Takeda A, Hasegawa K, Nakashima K, Yamamoto M, Hattori N, Murata M, Toda T	Calbindin 1, fibroblast growth factor 20, and α-synuclein in sporadic Parkinson's disease	Hum Genet	124	89-94	2008
Sato S, Omori Y, Katoh K, Kondo M, Kanagawa M, Miyata K, Funabiki K,	Pikachurin, a dystroglycan ligand, is essential for photoreceptor ribbon synapse formation	Nature Neurosci	11	923-931	2008

Koyasu T, Kajimura N, Miyoshi T, Sawai H, Kobayashi K, Tani A, Toda T, Usukura J, Tano Y, Fujikado T, Furukawa T					
Fujikake N, Nagai Y, Popiel HA, Okamoto Y, Yamaguchi M, Toda T	Heat shock transcription factor 1-activating compounds suppress polyglutamine-induced neurodegeneration through induction of multiple molecular chaperones	J Biol Chem	283	26188-26197	2008
Wakayama Y, Inoue M, Kojima H, Yamashita S, Shibuya S, Jimi T, Hara H, Matsuzaki Y, Oniki H, Kanagawa M, Kobayashi K, Toda T	Reduced expression of sarcospan in muscles of Fukuyama congenital muscular dystrophy	Histol Histopathol	23	1425-1438	2008
Tomiyama H, Mizuta I, Li Y, Funayama M, Yoshino H, Li L, Murata M, Yamamoto M, Kubo SI, Mizuno Y, Toda T, Hattori N	LRRK2 P755L variant in sporadic Parkinson's disease	J Hum Genet	53	1012-1015	2008
Asanuma M, Miyazaki I, Diaz-Corrales FJ, Miyoshi K, Ogawa N, Murata M	Preventing effects of a novel anti-parkinsonian agent zonisamide on dopamine quinine formation	Neurosci Res	60	106-113	2008
Ota M, Sato N, Saito Y, Endo F, Murata M, Asada T	Diffusion tensor imaging in familial spastic paraplegia with mental impairment and thin corpus callosum	Magn Reson Med Sci	7(3)	163-167	2008
Okamoto T, Ogawa M, Lin Y, Murata M, Miyake S, Ymamura T	Treatment of neuromyelitis opica: Current debate	Ther Adv Neurol Disord	1	43-52	2008
Kobayashi A, Arima K, Ogawa M, Murata M	Plaque-type deposition of prion Protein in the damaged white matter of sporadic Creutzfeldt-Jakob disease MM1 patients	Acta Neuropathol	116	561-566	2008

Obi T, Nishioka K, Owen A. Ross OA, Terada T, Yamazaki K, Sugiura, A, Takanashi M, Mizoguchi K, Mori H, Mizuno Y, Hattori N	Clinicopathological study of a SNCA gene duplication patient with Parkinson disease and dementia	Neurology	70	238-241	2008
Ning Y, Kanai K, Tomiyama H, Li Y, Funayama M, Yoshino H, Sato S, Asahina M, Kuwabara S, Takeda A, Hattori T	PARK9-linked parkinsonism in Eastern Asia: Mutation detection in ATP13A2 and clinical phenotype	Neurology	70	1491-1493	2008
Ross OA, Wu YR, Lee MC, Funayama M, Chen ML, Soto AI, Mata IF, Lee-Chen GJ, Chen CM, Tang M, Zhao Y, Hattori N, Farrer MJ, Tan EK, Wu RM	Analysis of Lrrk2 R1628P as a risk factor for Parkinson's disease	Ann Neurol	64	88-92	2008
Funayama M, Li Y, Tsoi TH, Lam CW, Ohi T, Yazawa S, Uyama E, Djaldetti R, Melamed E, Yoshino H, Imamichi Y, Takashima H, Nishioka K, Sato K, Tomiyama H, Kubo S, MD, Mizuno Y, Hattori N	Familial parkinsonism with digenic *parkin* and *PINK1* mutations	Mov Disord	23	1461-1465	2008
Tomiyama H, Kokubo Y, Sasaki R, Li Y, Imamichi Y, Funayama M, Mizuno Y, Hattori N, Kuzuhara S	Mutation analyses in amyotrophic lateral sclerosis/parkinsonism-dementia complex of the Kii peninsula, Japan	Mov Disord	23	2344-2348	2008
Ross OA, Braithwaite AT, Skipper LM, Kachergus J, Hulihan MM, Middleton FA, Nishioka K, Fuchs	Genomic investigation of alpha-synuclein multiplication and parkinsonism	Ann Neurol	63	743-750	2008

J, Gasser T, Maraganore DM, Adler CH, Chartier-Harlin MC, Nilsson C, Langston JW, Gwinn-Hardy K, Hattori N, Farrer MJ					
Mizuno Y, Hattori N, Kubo SI, Sato S, Nishioka K, Hatano T, Tomiyama H, Funayama M, Machida Y, Mochizuki H	Progress in the pathogenesis and genetics of Parkinson's disease	Philos Trans R Soc Lond B Biol Sci	363	2215-2227	2008
Popiel HA, Nagai Y, Fujikake N, Toda T	Delivery of the aggregate inhibitor peptide QBP1 into the mouse brain using PTDs and its therapeutic effect on polyglutamine disease mice	Neurosci Lett	449	87-92	2009
Kanagawa M, Nishimoto A, Chiyonobu T, Takeda S, Miyagoe-Suzuki Y, Wang F, Fujikake N, Taniguchi M, Lu Z, Tachikawa M, Nagai Y, Tashiro F, Miyazaki J, Tajima Y, Takeda S, Endo T, Kobayashi K, Campbell KP, Toda T	Residual laminin-binding activity and enhanced dystroglycan glycosylation by LARGE in novel model mice to dystroglycanopathy	Hum Mol Genet	18	621-631	2009
Okamoto Y, Nagai Y, Fujikake N, Popiel HA, Yoshioka T, Toda T, Inui T	Surface plasmon resonance characterization of specific binding of polyglutamine aggregation inhibitors to the expanded polyglutamine stretch	Biochem Biophys Res Commun	378	634-639	2009
Tomita K, Popiel HA, Nagai Y, Toda T, Yoshimitsu Y, Ohno H, Oishi S, Fujii N	Structure-activity relationship study on polyglutamine binding peptide QBP1	Bioorg Med Chem	17	1259-1263	2009
Mitsui J, Mizuta I, Toyoda A, Ashida R, Takahashi Y, Goto J, Fukuda Y, Date H, Iwata A, Yamamoto M,	Mutations for Gaucher disease confer a high susceptibility to Parkinson disease	Arch Neurol	66	571-576	2009

Hattori N, Murata M, Toda T, Tsuji S					
Shikishima C, Hiraishi K, Yamagata S, Sugimoto Y, Takemura R, Ozaki K, Okada M, Toda T, Ando J	Is g an entity? A Japanese twin study using syllogisms and intelligence tests	Intelligence	37	256-267	2009
Murata M	Levodopa in the early treatment of Parkinson's disease	Parkinsonism & Related Disorders	15(1)	S17-S20	2009
Mellick GD, Siebert GA, Funayama M, Buchanan DD, Li Y, Imamichi Y, Yoshino H, Silburn PA, Hattori N	Screening PARK Genes for Mutations in Early Onset Parkinson's Disease Patients from Queensland, Australia	Parkinsonism & Related Disorders	15	105-109	2009
Momma K, Funayama M, Li Y, Ichinose H, Motoyoshi K, Hattori N, Mizuno Y, Kamakura K	A new mutation in the GCH1 gene presents as early-onset Parkinsonism	Parkinsonism & Related Disorders	15	160-161	2009
Saitsu H, Kurosawa K, Kawara H, Eguchi M, Mizuguchi T, Harada N, Kaname T, Kano H, Miyake N, Toda T, Matsumoto N	Characterization of the complex 7q21.3 rearrangement in a patient with bilateral split-foot malformation and hearing loss	Am J Med Genet	149A	1224-1230	2009
Xiong H, Wang S, Kobayashi K, Jiang Y, Wang J, Chang X, Yuan Y, Liu J, Toda T, Fukuyama Y, Wu X	Fukutin gene retrotransposal insertion in a non-Japanese Fukuyama congenital muscular dystrophy (FCMD) patient	Am J Med Genet	149A	2403-2408	2009
Sidransky E, Nalls MA, Aasly JO, Aharon-Peretz J, Annesi G, Barbosa ER, Bar-Shira A, Berg D, Bras J, Brice A, Chen CM, Clark LN, Condroyer C, De Marco EV, Dürr A, Eblan MJ, Fahn S, Farrer MJ, Fung HC, Gan-Or Z,	Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease	N Engl J Med	361	1651-1661	2009

Gasser T, Gershoni-Baruch R, Giladi N, Griffith A, Gurevich T, Januario C, Kropp P, Lang AE, Lee-Chen GJ, Lesage S, Marder K, Mata IF, Mirelman A, Mitsui J, Mizuta I, Nicoletti G, Oliveira C, Ottman R, Orr-Urtreger A, Pereira LV, Quattrone A, Rogaeva E, Rolfs A, Rosenbaum H, Rozenberg R, Samii A, Samaddar T, Schulte C, Sharma M, Singleton A, Spitz M, Tan EK, Tayebi N, Toda T, Troiano AR, Tsuji S, Wittstock M, Wolfsberg TG, Wu YR, Zabetian CP, Zhao Y, Ziegler SG					
Satake W, Nakabayashi Y, Mizuta I, Hirota Y, Ito C, Kubo M, Kawaguchi T, Tsunoda T, Watanabe M, Takeda A, Tomiyama H, Nakashima K, Hasegawa K, Obata F, Yoshikawa T, Kawakami H, Sakoda S, Yamamoto M, Hattori N, Murata M, Nakamura Y, Toda T	Genome-wide association study identifies common variants at four loci as genetic risk factors for Parkinson's disease	Nature Genet	41	1303-1307	2009
Fukae J, Sato S, Shiba K, Sato K, Mori H, Sharp PA, Mizuno Y, & Hattori N	Programmed cell death-2 isoform1 is ubiquitinated by parkin and increased in the substantia nigra of patients with autosomal recessive Parkinson's disease	FEBS Lett	383	521-525	2009
Sasaki K, Shimura H, Itaya M, Tanaka	Excitatory amino acid transporter 2 associates	FEBS Lett	583	2194-200	2009

R, Mori H, Mizuno Y, Kosik KS, Tanaka S, Hattori N	with phosphorylated tau and is localized in neurofibrillary tangles of tauopathic brains				
Tomiyama H, Li Y, Yoshino H, Mizuno Y, Kubo S, Toda T, Hattori N	Mutation analysis for DJ-1 in sporadic and familial parkinsonism: Screening strategy in parkinsonism	Neurosci Lett	455	159-161	2009
Antonini A, Tolosa E, Mizuno Y, Yamamoto M, Poewe WH	A reassessment of risks and benefits of dopamine agonists in Parkinson's disease	Lancet Neurol.	8	929 - 937	2009
Zabetian CP, Yamamoto M, Lopez AN, Ujike H, Mata IF, Izumi Y, Kaji R, Maruyama H, Morino H, Oda M, Hutter CM, Edwards KL, Schellenberg GD, Tsuang DW, Yearout D, Larson EB, Kawakami H	LRRK2 mutations and risk variants in Japanese patients with Parkinson's disease	Mov Disord	24	1034-1041	2009
Kogo H, Kowa H, Yamada K, Bolor H, Tsutsumi M, Ohye T, Inagaki H, Taniguchi M, Toda T, Kurahashi K	Screening of genes involved in chromosome segregation during meiosis I: towards the identification of genes responsible for infertility in humans	J Hum Genet	55	293-299	2010
Tan EK, Kwok HH, Tan LC, Zhao WT, Prakash KM, Au WL, Pavanni R, Ng YY, Satake W, Zhao Y, Toda T, Liu JJ	Analysis of GWAS-linked loci in Parkinson disease reaffirms PARK16 as a susceptibility locus	Neurology	75	508-512	2010
Saitoh Y, Ogawa M, Naito Y, Komatsuzaki Y, Tagaya H, Arima K,Tamaoka A, Kitamoto T, Murata M	Discordant clinicopathological phenotypes in a Japanese kindred of fatal familial insomnia	Neurology	74	86-89	2010
Kawajiri S, Saiki S, Sato S, Sato F, Hatano T, Eguchi H, Hattori N	PINK1 is recruited to mitochondria with parkin and associates with LC3 in mitophagy	FEBS Lett.	584	1073-1079	2010
Krüger R, Sharma M, Riess O, Gasser T, Van Broeckhoven C,	A large-scale genetic association study to evaluate the contribution of Omi/HtrA2 (PARK13) to	Neurobiol Aging	in press		

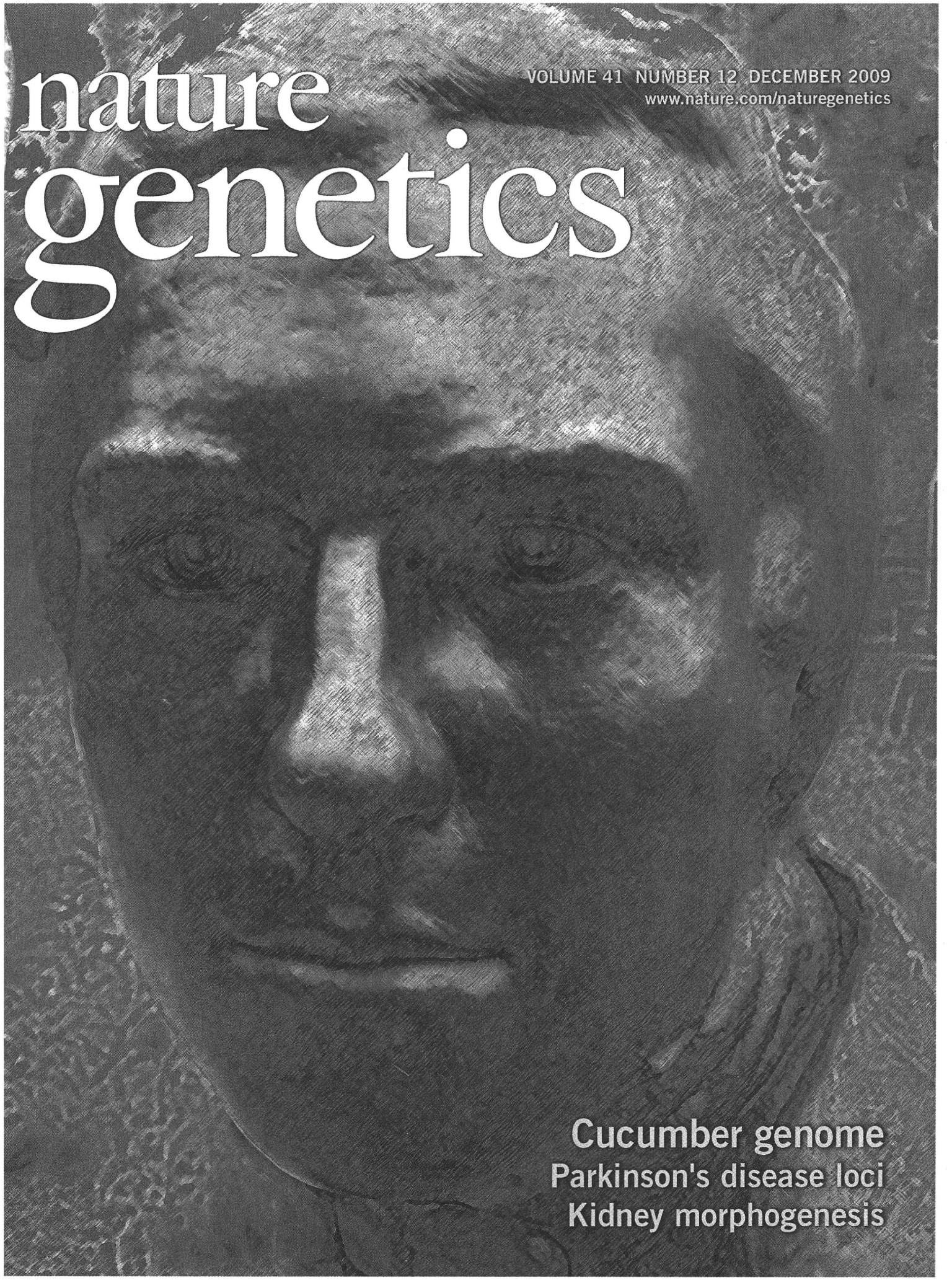
Theuns J, Aasly J, Annesi G, Bentivoglio AR, Brice A, Djarmati A, Elbaz A, Farrer M, Ferrarese C, Gibson JM, Hadjigeorgiou GM, Hattori N, Ioannidis JP, Jasinska-Myga B, Klein C, Lambert JC, Lesage S, Lin JJ, Lynch T, Mellick GD, de Nigris F, Opala G, Prigione A, Quattrone A, Ross OA, Satake W, Silburn PA, Tan EK, Toda T, Tomiyama H, Wirdefeldt K, Wszolek Z, Xiromerisiou G, Maraganore DM; for the Genetic Epidemiology of Parkinson's disease consortium	Parkinson's disease				
永井義隆　ポピエル明子　藤掛伸宏　戸田達史	ポリグルタミン病に対する治療戦略	BRAIN NERVE	59	393-404	2007
戸田達史	パーキンソン病の分子遺伝学	BRAIN NERVE	59	815-823	2007
戸田達史	班会議に行こう？贈る言葉あれこれ	分子細胞治療	6	494	2007
戸田達史	神経疾患とゲノム	最新医学	62S	2153-2163	2007
戸田達史	福山型遺伝子フクチン同定のヒント，幸運とそれから	臨床神経学	47	743-748	2007
戸田達史	ポストゲノム時代の神経疾患の分子遺伝学	神経治療学	24	641-645	2007
村田美穂	パーキンソン病の治療戦略　早期患者への治療方針	内科	99	787-791	2007
村田美穂	薬物治療：我が国初の新規治療薬の開発に向けて - 新規抗パーキンソン病薬ゾニサミドの開発 -	最新医学	62	1612-1617	2007
村田美穂	ジストニアの内科的治療の現状	神経内科	67	62-65	2007
村田美穂	抗てんかん薬 zonisamide の Parkinson 病に対する効果	医学のあゆみ	222	829-830	2007

村田美穂	話題のくすり　エンタカポン	日本病院薬剤師会雑誌	43	1579-1582	2007
青木吉嗣　山本敏之　尾方克久　大矢　寧　小川雅文　村田美穂	嚥下造影検査が重症筋無力症増悪の評価に有効であった１例	臨床神経学	47	669-671	2007
戸田達史	福山型先天性筋ジストロフィー	Clin Neurosci	26	163-167	2008
戸田達史	福山型筋ジストロフィー	ビジュアル疾患解説　眼で見る遺伝病とターナー症候群	2	6-7	2008
戸田達史	孤発性パーキンソン病のゲノムワイドスクリーニング	ゲノム医学	8	105-110	2008
小林千浩　戸田達史	認知と遺伝子	Cognition and Dementia	7	35-43	2008
谷口真理子　戸田達史	筋ジストロフィー	小児内科	40	1308-1314	2008
水田依久子　戸田達史	孤発性パーキンソン病のメカニズム	成人病と生活習慣病	38	887-892	2008
戸田達史	Alzheimer 病と遺伝	成人病と生活習慣病	38	1205-1210	2008
戸田達史	福山型筋ジストロフィーの発見とその類縁疾患における病態	蛋白質　核酸　酵素	53	1771-1780	2008
村田美穂	パーキンソン病治療薬の問題点と今後望まれる薬剤	日本病院薬剤師会雑誌	131	281-284	2008
村田美穂	パーキンソン病における併用療法のあり方と注意点	老年医学	46	365-369	2008
村田美穂	パーキンソン病薬物療法のメリット・デメリット	医学のあゆみ	225	395-399	2008
岡本智子　村田美穂	プライマリケア時代の症候の診方―振戦―	診断と治療増刊号	96	149-155	2008
村田美穂	ゾニサミドの抗パーキンソン病効果	成人病と生活習慣病	38	967-970	2008
村田美穂	パーキンソン病治療の変遷と今後の展望　薬物療法L-dopaの効果と安全性に関する最近の知見	Prog. Med.	28	2347-2350	2008
村田美穂	パーキンソン病の治療―薬物療法の up to date―	臨床神経学	48	986-988	2008
村田美穂　久野貞子	パーキンソン病におけるＤＢＳアンケート結果―満足度と問題点―	Pharma Medica	26	6-11	2008
村田美穂	パーキンソン病	ドクターサロン	52	177-180	2008
村田美穂	パーキンソン病　最新情報	今日の健康	7	114-121	2008
服部信孝	遺伝性パーキンソン病の	脳２１	11	372-376	2008

	遺伝子産物の機能解析から黒質神経変性のメカニズムを探る				
服部信孝 久保紳一郎	ここまでわかったパーキンソン病(PD)の成因　遺伝性PDの病態からわかったこと	臨床神経学	47	774-778	2008
水田依久子 戸田達史 澤田誠	家族性パーキンソン病は孤発性パーキンソンのモデルになるか？	Frontiers in Parkinson Disease	2	79-87	2009
戸田達史	パーキンソン病関連遺伝子の全ゲノム関連解析	最新医学	64	872-879	2009
戸田達史	パーキンソン病のゲノムワイド関連解析	細胞	41	198-202	2009
戸田達史	福山型先天性筋ジストロフィー	小児科	50	899-906	2009
戸田達史 佐竹渉 水田依久子	関連遺伝子 疾患感受性遺伝子の同定	日本臨床	67 増刊号 4	83-90	2009
三井純 戸田達史	孤発性パーキンソン病の分子遺伝学	実験医学	27 増刊号 12	1854-1859	2009
戸田達史	パーキンソン病のゲノミックス	老年精神医学雑誌	20	973-979	2009
戸田達史	福山型筋ジストロフィーおよび類縁疾患の病態・治療戦略	臨床神経学	49	859-862	2009
村田美穂	パーキンソン病の薬物治療—最近の知見	日本医事新報	4419	105	2009
村田美穂	パーキンソン病の薬物治療	BRAIN and NERVE	61	464-472	2009
村田美穂	脊髄小脳変性症　薬物療法	Clinical Neuroscience	27	92－94	2009
村田美穂	神経救急－見落としがちな神経疾患を中心に－薬剤性パーキンソン病の抗コリン薬の使用は必ずしも効果があるとは限らない	Clinical Neuroscience	27	946	2009
村田美穂	パーキンソン病患者のUnmet Needs, 医療連携の重要性	Pharma Medica	27	117-124	2009
村田美穂	パーキンソン病の四大徴候～パーキンソン病診断のコツとPitfall～	Frontiers in Parkinson Disease	2	92－95	2009
村田美穂	パーキンソン病—基礎・臨床研究のアップデート— 薬物療法 新規治療薬－ゾニサミド－	日本臨牀	67	401-405	2009
山本敏之　大矢寧　古澤嘉彦　埜中征哉　村田美穂	反復する無自覚性低血糖の治療にPioglitazoneが有効であった筋強直性ジストロフィーの1例	臨床神経	49	641-645	2009
千原典夫　山本	脊椎後彎と食道裂孔ヘ	臨床神経	49	493-496	2009

敏之　林幼偉 塚本忠　小川雅文　村田美穂	ルニアがレボドパ吸収に影響したパーキンソン病の82歳女性例				
戸田達史	筋ジストロフィーの最新検査	SRL 宝函	30(4)	4-11	2010
戸田達史 佐竹渉	孤発性パーキンソン病のリスク遺伝子	最新医学	65	806-813	2010
戸田達史 佐竹渉	ゲノムワイド関連解析によるパーキンソン病リスク遺伝子の同定	医学のあゆみ	233	640-642	2010
戸田達史	パーキンソン病の GWAS	Bio Clinica	25	477-482	2010
戸田達史	福山型筋ジストロフィーの治療戦略	難病と在宅のケア	16	41-43	2010
戸田達史	福山型筋ジストロフィー	JFNMH Newsletter	7	2-6	2010
小田哲也　苅田典生　濱口浩敏 田中惠子　戸田達史	抗 aquaporin-4 抗体陽性症例の治療経験	神経内科	73	194-198	2010
戸田達史	疾患感受性遺伝子	Current Therapy	28	859-860	2010
村田美穂	新しい抗パーキンソン病薬ゾニサミドの発見	臨床神経	50	67-72	2010

IV. 研究成果の刊行物・別刷



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Parkinson's disease loci
Kidney morphogenesis

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Genome-wide association study identifies common variants at four loci as genetic risk factors for Parkinson's disease

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To identify susceptibility variants for Parkinson's disease (PD), we performed a genome-wide association study (GWAS) and two replication studies in a total of 2,011 cases and 18,381 controls from Japan. We identified a new susceptibility locus on 1q32 ($P = 1.52 \times 10^{-12}$) and designated this as *PARK16*, and we also identified *BST1* on 4p15 as a second new risk locus ($P = 3.94 \times 10^{-9}$). We also detected strong associations at *SNCA* on 4q22 ($P = 7.35 \times 10^{-17}$) and *LRRK2* on 12q12 ($P = 2.72 \times 10^{-8}$), both of which are implicated in autosomal dominant forms of parkinsonism. By comparing results of a GWAS performed on individuals of European ancestry, we identified *PARK16*, *SNCA* and *LRRK2* as shared risk loci for PD and *BST1* and *MAPT* as loci showing population differences. Our results identify two new PD susceptibility loci, show involvement of autosomal dominant parkinsonism loci in typical PD and suggest that population differences contribute to genetic heterogeneity in PD.

Parkinson's disease (MIM168600) is one of the most common neurodegenerative diseases worldwide, affecting 1–2% of individuals aged ≥65 years[1]. Clinical features of PD result primarily from loss of dopaminergic neurons in the substantia nigra. Various medical treatments improve PD symptoms but do little to deter disease progression. Identifying genetic risk factors for PD will be helpful in elucidating the pathogenesis of the disease. Linkage studies have been successful in mapping genes for mendelian forms of parkinsonism: *SNCA* (encoding α-synuclein)[2] and *LRRK2* (refs. 3,4) in autosomal dominant forms, and *PARK2* (encoding parkin), *PINK1*, *PARK7* (encoding DJ-1) and *ATP13A2* in autosomal recessive forms[5,6]. However, mendelian forms of parkinsonism are rare compared to the far more common typical PD, a complex disorder caused by multiple genetic and environmental factors[7]. Association studies have evaluated variants in many candidate genes for PD[7], but only a few, such as common variants of *SNCA*[8–10] and rare mutations of *GBA*[11], have been identified as PD-susceptibility genes with genome-wide significance. Recently, GWASs in PD have provided association evidence at several loci, but not at the genome-wide significant level[12–14].

We conducted a GWAS and two subsequent replication studies for PD to identify further common variants that contribute to disease. In the GWAS stage, we genotyped 561,288 SNPs on autosomal and sex chromosomes using the HumanHap550 array (Illumina). The GWAS stage included 1,078 PD cases and 2,628 controls in the Japanese population (**Supplementary Note**). After SNP and sample quality control analyses, we used genotype data from 435,470 SNPs in 988 cases and 2,521 controls in the GWAS analysis (see Online Methods).

We tested for association between each SNP and PD using the Cochran-Armitage trend test with 1 d.f. The quantile-quantile plot showed a close match to test statistics expected under the null distribution (genomic inflation factor $\lambda = 1.055$ for PD) (**Fig. 1a,b**). This indicates minimal overall inflation of genome-wide statistical results due to population stratification and also reveals a number of SNPs whose *P* values exceed those expected under the null hypothesis. Seventeen SNPs showed $P < 5 \times 10^{-7}$, the threshold for genome-wide significance suggested by the Wellcome Trust Case Control Consortium[15] (**Fig. 1c**). All these SNPs were located on 4q22, a region harboring *SNCA* that was previously identified by us and others as a definite susceptibility gene for PD[8–10].

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