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
富田博秋.	遺伝子発現解析研究の実際～ブレインバンク運営に求められている品質管理とは	加藤忠史	脳バンク　精神疾患の謎を解くために	光文社	東京	2011	167-176
富田博秋.	求められるブレインバンクの姿　～ブレインバンクは実際に何をするのか～	加藤忠史	脳バンク　精神疾患の謎を解くために	光文社	東京	2011	237-245
富田博秋	精神神経疾患死後脳のバイオリソース整備. ,.	独立行政法人科学技術振興機構	研究開発戦略センター国際比較調査報告書2011年版	独立行政法人科学技術振興機構	東京	2011	126-129
富田博秋、小野千晶、兪志前	. 統合失調症の陰性症状の進行に関わる精神神経免疫学的メカニズムに関する研究	財団法人　精神・神経科学振興財団	こころの健康と病気2010年版	財団法人精神・神経科学振興財団	東京	2011	119-131
黒澤健司.	確定診断とその進め方	福嶋義光	遺伝子医学MOOK別冊「遺伝カウンセリングハンドブック」	メディカルドウ	大阪	2011	58-59
黒澤健司.	先天奇形、先天奇形症候群、Dysmorphology.	福嶋義光	遺伝子医学MOOK別冊「遺伝カウンセリングハンドブック」	メディカルドウ	大阪	2011	76-79
黒澤健司.	予想外の結果が得られた場合：次世代シークエンス	福嶋義光	遺伝子医学MOOK別冊「遺伝カウンセリングハンドブック」	メディカルドウ	大阪	2011	345-347
福與なおみ、高橋利幸、藤原一男	視神経脊髄炎	塩見正司	小児科臨床ピクシス28「急性脳炎・急性脳症」	診断と治療社	東京	2011	
黒澤健司	染色体異常の理解	千代豪昭	臨床遺伝学講義ノート	オーム出版社	東京	2010	37-49
古谷憲孝, 黒澤健司	口唇口蓋裂の遺伝	小林眞司	胎児診断から始まる口唇口蓋裂 —集学的治療のアプローチ—	メディカルビュー社	東京	2010	32-38

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
Yoneda Y, Saitsu H, Touyama M, Makita Y, Miyamoto A, Hamada K, Kurotaki N, Tomita H, Nishiyama K, Tsurusaki Y, Doi H, Miyake N, Ogata K, Naritomi K, Matsumoto N.	Missense mutations in the DNA-binding/dimerization domain of NFIX cause Sotos-like features.	J Hum Genet.	57(3)	207-211	2012
Yu Z, Ono C, Kim HB, Komatsu H, Tanabe Y, Sakae N, Nakayama KI, Matsuoka H, Sora I, Bunney WE, Tomita H.	Four mood stabilizers commonly induce FEZ1 expression in human astrocytes	Bipolar Disorders	13(5-6)	486-499	2011
Yu Z, Ono C, Sora I, Tomita H	Effect of chronic lithium treatment on gene expression profile in mouse microglia and brain dendritic cells	Japanese Journal of Neuropsychopharmacology	31 (2)	101-102	2011
Saitsu H, Osaka H, Sasaki M, Takanashi J, Hamada K, Yamashita A,et., al., Matsumoto N.	Mutations in POLR3A and POLR3B encoding RNA polymerase III subunits cause an autosomal recessive hypomyelinating leukoencephalopathy.	Am J Hum Genet	in press		
Yoneda Y, Haginoya K, Arai H, Tsurusaki Y, et. al. , Matsumoto N, Saitsu H.	De novo and inherited mutations in the gene encoding PORE (tentative name) cause porencephaly.	Am J Hum Genet	in press		
Doi H, Yoshida K, T Yasuda, Fukuda M, Fukuda Y, et. al., Matsumoto N.	Exome sequencing reveals a homozygous SYT14 mutation in adult-onset autosomal recessive spinocerebellar ataxia with psychomotor retardation.	Am J Hum Genet	89(2)	320-327	2011
Okada I, Hamanoue H, Terada K, et. al., Matsumoto N, Saitsu H.	SMOC1 is essential for ocular and limb development in humans and mice.	Am J Hum Genet	88(1)	30-41	2011
Saitsu H, Osaka H, Sugiyama S, Kurosawa K, et., al., Kato M, Matsumoto N.	Early infantile epileptic encephalopathy associated with the disrupted gene encoding Slit-Robo Rho GTPase activating protein 2 (SRGAP2).	Am J Med Genet	in press		
Saitsu H, Kato M, Shimono M, Senju A, et. al., Matsumoto N.	Association of genomic deletions in the STXBP1 gene with Ohtahara 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
Saitsu H, Igarashi N, Mitsuhiro Kato M, et. al., Hayasaka K, Matsumoto N.	De novo 5q14.3 translocation 121.5-kb upstream of MEF2C in a patient with severe mental retardation and early-onset epileptic encephalopathy.	Am J Med Genet	in press		
Kosho T, Miyake N, Mizumoto S, Hatamochi A, Fukushima Y, Sugahara K, Matsumoto N.	A response to: Loss of dermatan-4-sulfotransferase 1 (D4ST1/CHST14) function represents the first dermatan sulfate biosynthesis defect, "Dermatan sulfate-deficient adducted thumb–clubfoot syndrome". Which name is appropriate, "Adducted thumb–clubfoot syndrome" or "Ehlers–Danlos syndrome"?	Hum Mut	in press		
Saitsu H, Osaka H, Nishiyama K, Tsurusaki Y, Doi H, Miyake N, Matsumoto N.	A girl with early-onset epileptic encephalopathy associated with microdeletion involving CDKL5., in press	Brain Dev	in press		
Sakai H, Suzuki S, Mizuguchi T, Imoto K, Doi H, Kikuchi M, Tsurusaki T, Saitsu H, Miyake N, Masuda M, Matsumoto N.	Rapid detection of gene mutations responsible for non-syndromic aortic aneurysm and dissection using two different methods: resequencing microarray technology and next-generation sequencing.	Hum Genet	in press		
Abdel-Salam GMH, Miyake N, Eid MM, Abdel-Hamid MS, Hassan NA, Eid OM, Effat LK, El-Badry TH, El-Kamah GY, El-Darouti M, Matsumoto N.	A homozygous Mutation in RNU4ATAC as a cause of microcephalic osteodysplastic primordial dwarfism type I (MOPD I) with associated pigmentary disorder.	Am J Med Genet	in press		
Miyatake S, Miyake N, Touho H, et. al. Matsumoto N.	Homozygous c.14576G>A variant of RNF213 predicts early-onset and severe form of moyamoya disease.	Neurology,	in press		
Tohyama J, Kato M, N, Kawasaki S, Kawara H, Matsui T, Akasaka N, Ohashi T, Kobayashi Y, Matsumoto N.	Dandy-Walker malformation associated with heterozygous ZIC1 and ZIC4 deletion: Report of a new patient.	Am J Med Genet	155(1)	130-131	2011

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Furuichi T, Dai J, Cho T-J, et. al. Matsumoto N, et. al.	CANT1 is also responsible for Desbuquois dysplasia, type 2 and Kim variant.	J Med Genet	48(1)	32-37	2011
Saitsu H, Hoshino H, Kato M, rt, al., Matsumoto N.	Paternal mosaicism of a STXBP1 mutation in Ohtahara syndrome.	Clin Genet	80	484-488	2011
Yano S, Bagheri A, Watanabe Y, Moseley K, Nishimura A, Matsumoto N, Baskin B, Ray PN.	Familial Simpson-Golabi-Behmel syndrome: Studies of X-chromosome inactivation and clinical phenotypes in two female individuals with GPC3 mutations.	Clin Genet	80	466-471	2011
Nishimura-Tadaki A, Wada T, Bano G, et. al., Matsumoto N.	Breakpoint determination of X;autosome balanced translocations in four patients with premature ovarian failure.	J Hum Genet	56(2)	156-160	2011
Hiraki Y, Nishimura A, Hayashidani M, Terada Y, Nishimura G, Okamoto N, Nishina S, Tsurusaki Y, Doi H, Saitsu H, Miyake N, Matsumoto N.	A de novo deletion of 20q11.2-q12 in a boy presenting with abnormal hands and feet, retinal dysplasia, and intractable feeding difficulty.	Am J Med Genet	152(2)	409-414	2011
Tonoki H, Harada N, Shimokawa O, Yosozumi A, Monzaki K, Satoh K, Mika Kosaki R, Sato A, Matsumoto N, Iizuka S.	Axenfeld-Rieger anomaly and Axenfeld-Rieger syndrome: clinical, molecular-cytogenetic, and DNA array analyses on three patients with chromosomal defects at 6p25.	Am J Med Genet Part A:	155 (12)	2925-2932	2011
Tadaki H, Saitsu H, Nishimura-Tadaki A, et. al., Matsumoto N.	De novo 19q13.42 duplications involving NLRP gene cluster in a patient with systemic-onset juvenile idiopathic arthritis.	J Hum Genet	56	343-347	2011
Miyake N, Yamashita S, Kurosawa K, et. al. Matsumoto N.	A novel homozygous mutation of DARS2 may cause a severe LBSL variant.	Clin Genet	80(3)	293-296	2011
Tadaki H, Saitsu H, Kanegane H, Miyake N, et. al., Matsumoto N.	Exonic deletion of CASP10 in a patient presenting with systemic juvenile idiopathic arthritis, but not with autoimmune lymphoproliferative syndrome type IIa.	Int J Immunogenet	38	287-293	2011

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Tsurusaki Y, Osaka H, Hamanoue H, Shimbo H, Tsuji M, Doi H, Saitsu H, Matsumoto N, Miyake N.	Rapid detection of a mutation causing X-linked leukodystrophy by exome sequencing.	J Med Genet	48	606-609	2011
Narumi Y, Shiihara T, Yoshihasi H, et. al. Matsumoto N, Fukushima Y.	Hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC) in an infant with Down syndrome.	Clin Dysmorphol	20(3)	166-167	2011
Dai J, Kim O-K, Cho T-J, et.al. Matsumoto N, Ohashi H, Kamatani N, Nishimura G, Furuichi T, Takahashi A, Ikegawa S.	A founder mutation of CANT1 common in Korean and Japanese Desbuquois dysplasia.	J Hum Genet	56(5)	398-400	2011
Saitsu H, Matsumoto N.	Genetic commentary: De novo mutations in epilepsy.	Dev Med Child Neurol	9	806-807	2011
Shimizu K, Okamoto N, Miyake N, et. al. Matsumoto N, Kosho T.	Delineation of dermatan 4-O-sulfotransferase 1 deficient Ehlers-Danlos syndrome: Observation of two additional patients and comprehensive review of 20 reported patients.	Am J Med Genet	155(8)	1949-1958	2011
Tsurusaki Y, Okamoto N, Suzuki Y, Doi H, Saitsu H, Miyake N, Matsumoto N.	Exome sequencing of two patients in a family with atypical X-linked leukodystrophy.	Clin Genet	80	161-166	2011
Hannibal MC, Buckingham KJ, Ng SB, et.al. Matsumoto N, , et. al., Bamshad MJ.	Spectrum of MLL2 (ALR) mutations in 110 cases of Kabuki syndrome.:,	Am J Med Genet	155 (7)	1511-1516	2011
Nagase H, Ishikawa H, Nishikawa T, Kurosawa K, Itani Y, Yamanaka M.	Prenatl management of the fetus with lethal malformation: from a study of oligohydroamnios sequence.	Fetal and Pediatric Pathology	30	145-149	2011
Tachibana Y, Aida N, Enomoto K, Iai M, Kurosawa K.	A case of Sjögren-Larsson syndrome with minimal MR imaging findings facilitated by proton spectroscopy.	Pediatr Radiol,	Epub ahead of print		2011
Ozawa K, Ishikawa H, Maruyama Y, Nagata T, Nagase H, Itani Y, Kurosawa K, Yamanaka M.	Congenital omphalocele and polyhydramnios: A study of 52 cases.	Fetal Diagn Ther	Epub ahead of print		2011

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Soneda A, Teruya H, Furuya N, Yoshihashi H, Enomoto K, Ishikawa A, Matsui K, Kurosawa K.	Proportion of malformations and genetic disorders among cases encountered at a high-care unit in a children's hospital.	Eur J Pediatr	Epub ahead of print		2011
Kurosawa K, Tanoshima-Takei M, Yamamoto T, Ishikawa H, Masuno M, Tanaka Y, Yamanaka M.	Sirenomelia with a de novo balanced translocation 46,X,t(X;16)(p11.2;p12.3).	Cong Anom	in press		
Kurosawa K, Masuno M, Kuroki Y.	Trends in occurrence of twin births in Japan.	Am J Med Genet Part A	Epub ahead of print		2011
Saito Y, Kubota M, Kurosawa K, et. al.	Polymicrogyria and infantile spasms in a patient with 1p36 deletion syndrome.	Brain Dev	33	437-441	2011
Uematsu M, Haginoya K, Kikuchi A, et. al. Hino-Fukuyo NFujiwara I, Kure S.	Hypoperfusion in caudate nuclei in patients with brain–lung–thyroid syndrome.	J Neurol Sci	in press		
Hirose M, Haginoya K, Yokoyama H, Kikuchi A, Hino-Fukuyo N, et. al.	Progressive atrophy of the cerebrum in 2 Japanese sisters with microcephaly with simplified gyri and enlarged extraaxial space.	Neuropediatrics	42(4)	163-166	2011
Waga C, Okamoto N, Ondo Y, Fukumura-Kato R, Goto YI, Kohsaka S, Uchino S.	Novel variants of the SHANK3 gene in Japanese autistic patients with severe delayed speech development.	Psychiatr Genet	21	208-211	2011
Okamoto N, Hatsukawa Y, Shimojima K, Yamamoto T.	Submicroscopic deletion in 7q31 encompassing CADPS2 and TSPAN12 in a child with autism spectrum disorder and PHPV	Am J Med Genet A	155	1568-1573	2011
Hayashi S, Okamoto N, Chinen Y, Takanashi JI, Makita Y, Hata A, Imoto I, Inazawa J.	Novel intragenic duplications and mutations of CASK in patients with mental retardation and microcephaly with pontine and cerebellar hypoplasia (MICPCH).	Hum Genet	Epub ahead of print		2011

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Kawazu Y, Inamura N, Kayatani F, Okamoto N, Morisaki H.	Prenatal complex congenital heart disease with Loeys–Dietz syndrome	Cardiology in the Young	on line		2011
Naiki M, Mizuno S, Yamada K, Yamada Y, Kimura R, Oshiro M, Okamoto N, et.al	MBTPS2 mutation causes BRESEK/BRESHECK syndrome.	Am J Med Genet	on line		2011
Okamoto N, Tamura D, Nishimura G, Shimojima K, Yamamoto T	Submicroscopic deletion of 12q13 including HOXC gene cluster with skeletal anomalies and global developmental delay.	Am J Med Genet A	155	2997-3001	2011
Ono S, Yoshiura K, Kurotaki N, Kikuchi T, Niikawa N, Kinoshita A.	Mutation and copy number analysis in paroxysmal kinesigenic dyskinesia families.	Mov Disord	26(4)	761-763	2011
Kubo T, Horai S, Ozawa H, Kurotaki N.	A case of undiagnosed catecholaminergic polymorphic ventricular tachycardia presenting with ventricular fibrillation after administration of succinylcholine during anesthesia for modified electroconvulsive therapy.	Psychiatry Clin Neurosci	65(4)	397	2011
Kurotaki N, Nobata H, Nonaka S, Nishihara K, Ozawa H.	Three cases of schizophrenia showing improvement after switching to blonanserin.	Psychiatry Clin Neurosci	65(4)	396-397	2011
Kurotaki N, Tasaki S, Mishima H, Ono S, Imamura A, Kikuchi T, Nishida N, Tokunaga K, Yoshiura K, Ozawa H.	Identification of novel schizophrenia loci by homozygosity mapping using DNA microarray analysis.	PLoS one	6(5)	e20589	2011
Shiihara T, others, Matsumoto N, others	A case of Baraitser-Winter syndrome with unusual brain MRI findings of pachygyria, subcortical band heterotopia and periventricular heterotopias.	Brain Dev	32(6)	502-505	2010
Saitsu H, others, Matsumoto N	Dominant negative mutations in α-II spectrin cause early onset West syndrome with severe cerebral hypomyelination, spastic quadriplegia, and developmental delay.	Am J Hum Genet	86(6)	881-889	2010

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Saitsu H, others, Matsumoto N	*STXBP1* mutations in severe infantile epilepsies with suppression-burst pattern.	Epilepsia	51(12)	2397-2405	2010
Sakai H, others, Matsumoto N	Analysis of an insertion mutation in a cohort of 93 patients with spinocerebellar ataxia type 31 (SCA31) from Nagano, Japan.	Neurogenet	11(4)	409-415	2010
Osaka H, others, Matsumoto N, Inoue K	Disrupted SOX10 regulation of GJC2 transcription causes Pelizaeus-Merzbacher-Like Disease.	Ann Neurol	68(2)	250-254	2010
Nishimura A, others, Matsumoto N	*De novo* deletion of 1q24.3-q31.2 in a patient with severe growth retardation.	Am J Med Genet	152A(5)	1322-1325	2010
Komoike Y, others, Matsumoto N, others	Zebrafish gene knockdowns imply roles for human *YWHAG* in infantile spasms and cardiomegaly.	Genesis	48(4)	233-243	2010
Doi H, others, Matsumoto N, others	Siblings with the adult-onset slowly progressive type of pantothenate kinase-associated neurodegeneration and a novel mutation, Ile346Ser, in PANK2: Clinical features and (99m) Tc-ECD brain perfusion SPECT findings.	J Neurol Sci	290 (1-2)	172-176	2010
Miyake N, others, Matsumoto N	Loss of decorin dermatan sulfate impairing collagen bundle formation in a new type of Ehlers-Danlos syndrome.	Hum Mut	31(8)	966-974	2010
Kosho T, others, Matsumoto N	A New Ehlers-Danlos Syndrome With Craniofacial Characteristics, Multiple Congenital Contractures, Progressive Joint and Skin Laxity, and Multisystem Fragility-related Manifestations.	Am J Med Genet	152A (6)	1333-1346	2010
Kimura S, others, Matsumoto N, Ishibashi M	Rudimentary Claws and Pigmented Nail-like Structures on the Distal Tips of the Digits of *Wnt7a* Mutant Mice: *Wnt7a* Suppresses Nail-like Structure Development in Mice.	Birth Defects Res A Clin Mol Teratol	88(6)	487-496	2010

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Kanazawa K, others, Matsumoto N	Choreo-ballistic movements in a case carrying a missense mutation in syntaxin binding protein 1 gene.	Mov Disord	25(13)	2265-2267	2010
Ng S, others, Matsumoto N, others	Exome sequencing identifies *MLL2* mutations as a cause of Kabuki syndrome.	Nat Genet	42(9)	790-793	2010
Yamada-Okabe T, others, Matsumoto N	Functional characterization of the zebrafish *WHSC1*-related gene, a homologue of human *NSD2*.	Biochem Biophys Res Commun	402(2)	335-339	2010
Hosokawa S, others, Okamoto N	A case of Brachmann-de Lange syndrome with congenital diaphragmatic hernia and *NIPBL* gene mutation	Congenit Anom (Kyoto).	50	129-132	2010
Kobayashi T, others, Okamoto N, others	Molecular and clinical analysis of RAF1 in Noonan syndrome and related disorders: dephosphorylation of serine 259 as the essential mechanism for mutant activation.	Hum Mutat.	31	284-294	2010
Okamoto N, others, Yamamoto T.	Co-occurrence of Prader-Willi and Sotos syndromes.	Am J Med Genet A.	152A	2103-2109	2010
Komatsuzaki S, others, Okamoto N, others	Mutation analysis of the SHOC2 gene in Noonan-like syndrome and in hematologic malignancies.	J Hum Genet	55	801-809	2010
Takanashi J, others, Okamoto N, Barkovich AJ.	Neuroradiologic features of CASK mutations.	Am J Neuroradiol.	31	1619-1622	2010
Hayashi S, Imoto I, Aizu Y, Okamoto N, others	Clinical application of array-based comparative genomic hybridization by two-stage screening for 536 patients with mental retardation and multiple congenital anomalies.	J Hum Genet	2010 Oct 28. [Epub ahead of print]		2010

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Filges I, Shimojima K, Okamoto N, others	Reduced expression by SETBP1 haploinsufficiency causes developmental and expressive language delay indicating a phenotype distinct from Schinzel-Giedion syndrome.	J Med Genet	2010 Oct 30. [Epub ahead of print]		2010
Tsuyusaki Y, others, Kurosawa K.	1p36 deletion syndrome associated with Prader-Willi-like phenotype.	Pediatr Int	52	547-550	2010
Hino-Fukyo N, others, Tsuchiya S	A case of West syndrome eith remission of spasms following multiple cerebral hemorrhages.	Brain Dev			in press
Uematsu M, others, Hino-Fukuyo N, otheres	Unique discrepancy between cerebral blood flow and glucose metabolism in hemimegalencephaly.	Epilepsy Res	92(2-3)	201-8	2010
Wakusawa K, Haginoya K, Ishitobi M, Hino-Fukuyo N, others	The cytokine and chemokine profiles in rhabdomyolysis in a patient with Gucher disease type II.	Neuropediatrics	51(9)	1886-8,	2010
Takayanagai M, others, Hino-Fukuyo N, others.	Acute encephalopathy with a truncation mutation in the SCN1A gene: a case report.	Epilepsia	51(9)	1886-8	2010
Ono S, others, Kurotaki N, others	Failure to confirm CNVs as of aetiological significance in twin pairs discordant for schizophrenia.	Twin Res Hum Genet	13(5)	455-460	2010
Nishihara K, Kinoshita H, Kurotaki N, others	Could subclinical hypothyroidism cause periodic catatonia with delusional misidentification syndrome?	Psychiatry Clin Neurosci	64(3)	338	2010
富田博秋	統合失調症の死後脳研究の現状と展望	精神科治療学	26 (12)	1581-1587	2011
富田博秋	死後脳研究の展望と脳バンク	精神医学	52	367-376	2010
沼田有里佳、植松貢、福與なおみ、柿坂庸介、小林朋子、廣瀬三恵子、萩野谷和裕、土屋滋	咽頭筋麻痺を認めない咽頭頸部上腕型 Guillain-Barré 症候群の 1 例	脳と発達	43	482-485	2011

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
福與なおみ、高橋利幸、萩野谷和裕、植松貢、土屋滋、藤原一男	小児期発症の抗アクアポリン4抗体陽性症例の臨床像	脳と発達	43	359-365	2011
渡邊尚子，黒滝直弘，菊池妙子，小澤寛樹.	Olanzapine投与が全身痙攣発作の原因と考えられた統合失調症の1例.	精神科	18(3)	359-365	2011
田山達之，黒滝直弘，渡邊尚子，金替伸治，小澤寛樹，木下裕久.	慢性関節リウマチに対し投与した抗IL-6受容体抗体が精神病症状の出現に関与したと考えられた1症例.	臨床精神医学	40(10)	1387-1390	2011
黒滝直弘，中根秀之.	ソトス症候群の分子遺伝解析とサポートシステムの開発における課題	精神科	in press		
黒澤健司	神経線維腫症1型における分子細胞遺伝学的スクリーニング	日レ病会誌	1	35-37	2010
豊田将夫、齋藤明子、福與なおみ、他、土屋滋	複合的要因によりビタミンＤ欠乏性くる病を発症した重症心身障害児の1例	小児科臨床	63(5):	1039-1044,	2010
黒滝直弘，他， 小澤寛樹	ＤＮＡマイクロアレイを用いた統合失調症のホモ接合マッピング	精神薬療研究年報	42	31-32	2010
黒滝直弘	認知症とは(１)	そよかぜ	77	12-14	2010
黒滝直弘	認知症とは(２)	そよかぜ	78	12-13	2010

IV. 研究成果の刊行物・別刷

Journal of Human Genetics (2012) 57, 207–211

www.nature.com/jhg

ORIGINAL ARTICLE

Missense mutations in the DNA-binding/dimerization domain of *NFIX* cause Sotos-like features

Yuriko Yoneda[1], Hirotomo Saitsu[1], Mayumi Touyama[2], Yoshio Makita[3], Akie Miyamoto[4], Keisuke Hamada[5], Naohiro Kurotaki[6], Hiroaki Tomita[7], Kiyomi Nishiyama[1], Yoshinori Tsurusaki[1], Hiroshi Doi[1], Noriko Miyake[1], Kazuhiro Ogata[5], Kenji Naritomi[8] and Naomichi Matsumoto[1]

Sotos syndrome is characterized by prenatal and postnatal overgrowth, characteristic craniofacial features and mental retardation. Haploinsufficiency of *NSD1* causes Sotos syndrome. Recently, two microdeletions encompassing *Nuclear Factor I-X (NFIX)* and a nonsense mutation in *NFIX* have been found in three individuals with Sotos-like overgrowth features, suggesting possible involvements of *NFIX* abnormalities in Sotos-like features. Interestingly, seven frameshift and two splice site mutations in *NFIX* have also been found in nine individuals with Marshall–Smith syndrome. In this study, 48 individuals who were suspected as Sotos syndrome but showing no *NSD1* abnormalities were examined for *NFIX* mutations by high-resolution melt analysis. We identified two heterozygous missense mutations in the DNA-binding/dimerization domain of the NFIX protein. Both mutations occurred at evolutionally conserved amino acids. The c.179T>C (p.Leu60Pro) mutation occurred *de novo* and the c.362G>C (p.Arg121Pro) mutation was inherited from possibly affected mother. Both mutations were absent in 250 healthy Japanese controls. Our study revealed that missense mutations in *NFIX* were able to cause Sotos-like features. Mutations in DNA-binding/dimerization domain of NFIX protein also suggest that the transcriptional regulation is abnormally fluctuated because of *NFIX* abnormalities. In individuals with Sotos-like features unrelated to *NSD1* changes, genetic testing of *NFIX* should be considered.
Journal of Human Genetics (2012) **57**, 207–211; doi:10.1038/jhg.2012.7; published online 2 February 2012

Keywords: DNA-binding/dimerization domain; missense mutation; *NFIX*; Sotos syndrome

INTRODUCTION

Sotos syndrome (MIM #117550) is an overgrowth syndrome characterized by tall stature and/or macrocephaly, distinctive facial appearance and mental retardation.[1] A *de novo* t(5;8)(q35;q24.1) translocation in a patient with Sotos syndrome revealed disruption of *NSD1* at 5q35. Subsequent identification of nonsense, frameshift and submicroscopic deletion mutations of *NSD1* in patients with Sotos syndrome clearly showed that haploinsufficiency of *NSD1* causes Sotos syndrome.[2] *NSD1* encodes nuclear receptor-binding SET domain protein 1, which functions as a histone methyltransferase that activates and represses transcription through chromatin modification.[3] The diagnosis of Sotos syndrome is established by confirming *NSD1* abnormalities,[4] and abnormalities of *NSD1* causes up to 90% of Sotos syndrome cases. However, a part of patients with suspected Sotos syndrome are known to show no abnormalities in *NSD1*,[5] suggesting involvement of another gene.

Recently it was reported that two patients with Sotos-like overgrowth features possessed microdeletions encompassing *Nuclear Factor I-X (NFIX)* at 19p13.2. In addition, a nonsense mutation in *NFIX* was identified in one patient with Sotos-like features.[6] Interestingly, frameshift and donor-splice site mutations were also identified in Marshall–Smith syndrome (MIM 602535) that is osteochondysplasia syndrome characterized by accelerated skeletal maturation, relative failure to thrive, respiratory difficulties, mental retardation and unusual facial features.[7] Therefore, *NFIX* mutations could cause either Sotos-like features or Marshall–Smith syndrome. Whereas the transcripts possessing the nonsense mutation in a patient with Sotos-like features suffered from the nonsense-mediated mRNA decay, transcripts of mutated alleles (by a donor-spice site and two frameshift mutations) in patients with Marshall–Smith syndrome escaped from the nonsense-mediated mRNA decay surveillance and could be translated, suggesting that haploinsufficiency of *NFIX* leads to

[1]Department of Human Genetics, Yokohama City University Graduate School of Medicine, Yokohama, Japan; [2]Department of Pediatrics, Okinawa Child Development Center, Okinawa, Japan; [3]Education Center, Asahikawa Medical University, Asahikawa, Japan; [4]Department of Pediatrics, Hokkaido Asahikawa Habilitation Center for Disabled Children, Asahikawa, Japan; [5]Department of Biochemistry, Yokohama City University Graduate School of Medicine, Yokohama, Japan; [6]Department of Neuropsychiatry, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan; [7]Department of Biological Psychiatry, Tohoku University Graduate School of Medicine, Sendai, Japan and [8]Department of Medical Genetics, University of the Ryukyus Faculty of Medicine, Nishihara, Japan
Correspondence: Dr N Matsumoto, Department of Human Genetics, Yokohama City University Graduate School of Medicine, Fukuura 3-9, Kanazawa-ku, Yokohama 236-0004, Japan.
E-mail: naomat@yokohama-cu.ac.jp
Received 9 September 2011; revised 21 November 2011; accepted 5 January 2012; published online 2 February 2012

Sotos-like features and dominant-negative effects of the truncated NFIX proteins cause Marshall–Smith syndrome.[6]

In this study, we screened for *NFIX* mutations in 48 Japanese patients who were suspected as Sotos syndrome, but showed neither deletions nor mutations in *NSD1*. Detailed genetic and clinical data are presented.

MATERIALS AND METHODS

Subjects

A total of 48 patients suspected as Sotos syndrome were analyzed for *NFIX* mutations. *NSD1* investigation by sequencing and fluorescent *in situ* hybridization analysis was negative in these patients. In this study, the patients presenting with cardinal features of Sotos syndrome (specific craniofacial features, intellectual disability and overgrowth to same extent) but showing no *NSD1* abnormalities are referred as those with 'Sotos-like features'. Experimental protocols were approved by the Committee for Ethical issues at Yokohama City University School of Medicine. All individuals were investigated in agreement with the requirements of Japanese regulations.

Mutation analysis

Genomic DNA was isolated from peripheral blood leukocytes according to standard methods. DNA for mutation screening was amplified by illustra GenomiPhi V2 DNA Amplification Kit (GE Healthcare, Buckinghamshire, UK). Sequencing of exon 1 and high-resolution melting curve (HRM) analysis of exon 2–9 covering the *NFIX* coding region (GenBank accession number NM_002501.2) were performed. For exon 1, the 12 μl PCR mixture contained 30 ng DNA, 0.3 μM each primer, 0.4 mM each dNTP, 1× PCR buffer for KOD FX and 0.3 U KOD FX polymerase (Toyobo, Osaka, Japan). For exons 2–9, real-time PCR and HRM analysis were serially performed in 12 μl mixture on Rotor-Gene Q (QIAGEN, Hilden, Germany). For exon 7, the PCR mixture contained 30 ng DNA, 0.3 μM each primer, 0.4 mM each dNTP, 0.36 μl SYTO9 (Invitrogen, Carlsbad, CA, USA), 0.4 mM each dNTP, 1× PCR buffer for KOD FX and 0.3 U KOD FX polymerase (Toyobo). For the remaining exons, the PCR mixture contained 30 ng DNA, 0.25 μM each primer, 0.36 μl SYTO9 (Invitrogen), 0.2 mM each dNTP, 1× ExTaq buffer and 0.375 U ExTaq HS (Takara, Otsu, Japan). Primers and conditions of PCR are shown in Supplementary Table 1. The PCR products showing an aberrant melting curve were sequenced. All the novel mutations in DNA amplified by GenomiPhi were verified by sequencing of PCR products using genomic DNA as a template. Mutations were checked in 250 Japanese normal controls (500 alleles) by HRM analysis.

Parentage testing

For the family showing *de novo* mutations, parentage was confirmed by microsatellite analysis as previously described.[8] Biological parentage was judged if more than four informative markers were compatible and other uninformative markers showed no discrepancies.

Prediction of functional effect

The effect of the mutations for protein features was predicted by following web-based prediction tools: SIFT (http://sift.jcvi.org/), PolyPhen (http://genetics.bwh.harvard.edu/pph/), PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/), Mutation Taster (http://www.mutationtaster.org/) and Align GVGD (http://agvgd.iarc.fr/agvgd_input.php).

RESULTS

NFIX mutations

Two heterozygous missense mutations were identified. The c.179T>C (p.Leu60Pro) mutation in patient 1 were not found in her parents, indicating that the mutation occurred *de novo* (Figure 1a). Biological parentage was confirmed by several microsatellite markers (data not shown). The c.362G>C (p.Arg121Pro) mutation in patient 2 was found in his mother (Figure 1a). These two mutations occurred at evolutionary conserved amino acids (Figure 1b) and were absent in 250 Japanese normal controls. Interestingly, the missense changes were located in DNA-binding/dimerization domain of the NFIX protein (Figure 1c). Evaluation with web-based prediction tools strongly suggested that these substitutions are pathogenic (Supplementary Table 2).

Clinical information of the patients

Patient 1 is a product of unrelated healthy parents. The body weight at birth was 2816 g (−0.6 s.d.), height 48.8 cm (0 s.d.) and OFC 33.5 cm (+0.3 s.d.). Neonatal hypotonia was recognized. At 17 months of age, her weight was 9.24 kg (−0.5 s.d.), height 84.9 cm (+2 s.d.) and OFC 48 cm (+1.2 s.d.). The facial appearance showed long/narrow and triangular face, high forehead, midface hypoplasia, prominent ears, epicanthal folds, strabismus, down-slanting palpebral fissures, short nose with anteverted nares, prominent long philtrum, everted lower lip and narrow palate (Figure 1d). Large hands/feet, prominent fingertips, pectus excavatum were also noted. Her primary dentition started at 7 months of age and was completed by 17 months of age. Bone age was estimated as 3 years at 17 months of age and as 5 years at 3 years of age. Bullet-shaped phalanges, which are typical features of Marshall–Smith syndrome, were not observed. She was initially diagnosed as Sotos syndrome. She showed mental retardation and severe developmental delay with developmental quotients of 19. Scoliosis was noted at 18 months of age and surgically treated for several times. Complex partial seizures were noted at 4 years of age and were controlled with phenytoin and zonisamide. At present (17 years of age), prognathia was observed (Figure 1e). Her weight was 40 kg (−2 s.d.) and height 156.5 cm (−0.2 s.d.).

Patient 2 is a male at age of 20 years. The birth weight was 2938 g (−0.4 s.d.), height 51 cm (+0.8 s.d.) and OFC 35.5 cm (+1.4 s.d.). Respiratory insufficiency was noted, but no visceral malformations were pointed out. Bilateral tubing therapy was performed for recurrent bilateral exudative otitis media at 4 years of age. At 14 years of age, his weight was 58.1 kg (+0.6 s.d.) and height 185.7 cm (+3.5 s.d.). Mental retardation was evident as the IQ score (Tanaka–Binet intelligence test) was 59. Craniofacial features included high forehead, down-slanting palpebral fissures and prognathia. He was suspected as Sotos syndrome. His mother showed tall stature, suggesting that c.362G>C led to overgrowth in the mother. Unfortunately, further details of clinical features in the mother are unavailable. Clinical information of two patients is summarized in Table 1.

DISCUSSION

NFIX is a member of the nuclear factor I (NFI) family proteins, which are implicated as site-specific DNA-binding proteins known to function in viral DNA replication and gene expression regulation.[9] NFI proteins form homo- or heterodimers and bind to the palindromic DNA consensus sequence through its N-terminal DNA-binding/dimerization domain.[10] Point mutations in DNA-binding/dimerization domain of NFI protein have been shown to cause loss of dimerization, DNA-binding and replication activities,[11] highlighting the importance of structural integrity of DNA-binding/dimerization domain. It has been reported that the DNA binding domain of SMADs and NFI transcription factors shared considerable structural similarity, and the secondary structure of the DNA-binding domain of NFI was estimated based on that of SMADs.[12] In this study, we identified two heterozygous missense mutations, the c.179T>C (p.Leu60Pro) and the c.362G>C (p.Arg121Pro), in the DNA-binding/dimerization domain. Of note, two mutations are estimated to be localized within α-helical region of DNA-binding domain and at evolutionally conserved amino acids between SMADs and NFI.[12] In addition, two mutations cause substitutions to a proline residue,

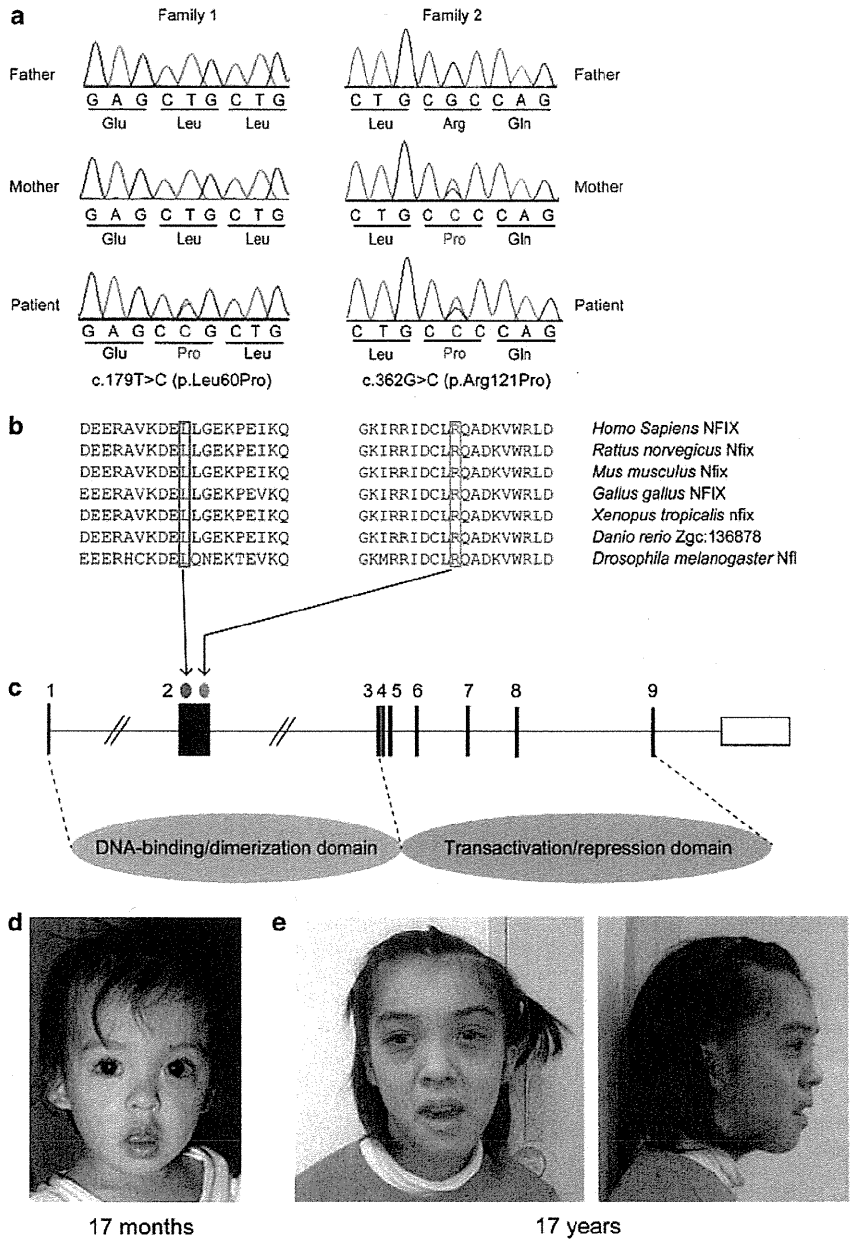

Figure 1 Missense mutations in *NFIX* in individuals with Sotos-like features. (**a**) Electropherogram of family 1 (left) and family 2 (right). The c.179T>C (p.Leu60Pro) mutation occured *de novo*. The c.362G>C (p.Arg121Pro) mutation was inherited from his mother. (**b**) An amino-acid sequence alignments of NFIX protein including amino-acid positions 60 and 121. Protein sequences were obtained through the NCBI protein database and multiple sequence alignment was performed by CLUSTALW web site (http://clustalw.ddbj.nig.ac.jp/). (**c**) Schematic representation of *NFIX* consisting of nine exons. UTR and coding exons are indicated by open and filled rectangles, respectively. The location of mutations is indicated by red (c.179T>C) and blue (c.362G>C) dots. At the bottom, C-terminal DNA-binding/dimerization domain and N-terminal transactivation/repression domain are depicted. Both the c.179T>C and c.362G>C mutations are located in exon 2 encoding a part of DNA-binding/dimerization domain. (**d**) Facial appearance of patient 1 at 17 months of age, showing long/narrow and triangular face, down slanting, short nose with anteverted nares and everted lower lip. (**e**) At 17 years of age, prognathia was noted in patient 1.

which is a unique amino acid characterized by imino radical. Proline has a pyrrolidine ring that restricts the available conformational space; therefore, it has effects on chain conformation and the process of protein folding.[13] Thus, it is very likely that two mutations could affect DNA-binding activity of NFIX protein through conformational changes of the DNA-binding domain.

Because *NFIX* mutations could cause both Marshall–Smith syndrome and Sotos-like features,[6] it is great concern to which of them two patients with missense mutations could be classified. Main clinical features of Sotos syndrome are childhood overgrowth including tall stature and/or macrocephaly, characteristic face and mental retardation. Other minor features are scoliosis, hypotonia in infancy, seizures,

Table 1 Clinical features of two patients with missense mutations in *NFIX*

				Reported by Malan et al.[6]		
		Patient 1	*Patient 2*	*Patient A*	*Patient B*	*Patient C*
Genetics	*NFIX deletion/mutation*	*c.179T>C*	*c.362G>C*	*del 19p13.3*	*del 19p13.3*	*c.568C>T*
Epidemiology	Age at last evaluation (years)	17	14	14	10	27
	Sex	F	M	M	M	F
	Mat/pat age	48/52	?/?	31/33	25/30	31/31
Prenatal growth	Birth weight (g)	2816 (−0.6 s.d.)	2938 (−0.4 s.d.)	4500 (>95)	3110 (10–50)	3600 (50–90)
	Birth height (cm)	48.8 (0 s.d.)	51 (+0.8 s.d.)	53 (95)	49 (50)	52 (95)
	OFC (cm)	33.5 (+0.3 s.d.)	35.5 (+1.4 s.d.)	38 (>95)	33.5 (10)	37.5 (>95)
Postnatal growth	Weight (kg)	9.24 (−0.5 s.d.)[a]	58.1 (+0.6 s.d.)[b]	>P98	>P98	>P98
	Height (cm)	84.9 (+2 s.d.)[a]	185.7 (+3.5 s.d.)[b]	>P98	>P98	>P98
Development						
SS	Autistic traits	−	−	+	+	+
	Behavioral anomalies	NA	−	+	+	+
	Motor retardation	+	+	+	−	−
	Hypotonia	+	+	+	+	−
Overlapped	Mental retardation	+	+	+	+	+
	Degree of delay	DQ19	IQ42	NA	NA	NA
	Speech delay	+	+	+	+	+
	First words (months)	24	18	NA	NA	NA
Craniofacial features						
SS	Long/narrow face	+	−	+	+	+
	Down-slanting palpebral fissures	+	+	+	−	+
	Small mouth	NA	−	+	−	+
	Prognathia	+	+	+	−	−
Overlapped	High forehead	+	+	+	+	+
MSS	Everted lower lip	+	−	+	−	+
	Underdeveloped midface	+	−	NA	NA	NA
	Proptosis	NA	−	NA	NA	NA
	Short nose	+	−	NA	NA	NA
	Prominent premaxilla	NA	−	NA	NA	NA
	Gum hypertrophy	+[c]	−	NA	NA	NA
	Retrognathia	−	−	NA	NA	NA
Eyes						
SS	Hypermotropia	−	−	+	+	−
	Strabismus	+	−	+	−	+
	Nystagmus	−	−	−	−	+
	Astigmatism	NA	NA	−	+	−
MSS	Myopia	NA	−	NA	NA	NA
	Blue sclerae	NA	−	NA	NA	NA
Musculo-skeletal abnormalities						
SS	Abdominal wall hypotonia	−	−	+	−	+
	Pectus excavatum	+	−	+	+	−
	Coxa valga	−	−	+	+	−
Overlapped	Scoliosis	+	−	+	−	+
	Advanced bone age	+	NA	+	+	+
MSS	Abnormal bone maturation	NA	NA	NA	NA	NA
	Bone fractures	−	−	NA	NA	NA
	Kyphosis	−	−	NA	NA	NA
	Umbilical hernia	−	−	NA	NA	NA

Abbreviations: F, female; M, male; Mat/pat, maternal/paternal; MSS, Marshall–Smith syndrome; NA, not ascertained; OFC, Occipitofrontal circumference; SS, Sotot's syndrome.
Growth of patients 1 and 2 is indicated with s.d. and that of patients in the report of Malan *et al.*[6] is indicated with percentile.
[a]At 17 months.
[b]At 14 years.
[c]Suggested the possibility of the adverse drug reaction.

cardiac defect and genitourinary anomalies.[5] On the other hand, main clinical features of Marshall–Smith syndrome are moderate to severe developmental delay with absent or limited speech, unusual behavior, disharmonic bone maturation, respiratory compromise secondary to upper airway obstruction, short stature and kyphoscoliosis.[14] One of remarkable differences between Sotos syndrome and Marshall–Smith syndrome is facial appearances. Although both syndromes has high forehead, Sotos syndrome has a long/narrow face, triangular shaped face with a prominent chin, down-slanting of the palpebral fissures,[1,4–5] whereas Marshall–Smith syndrome has proptosis, underdeveloped midface and prominent premaxilla.[7,14] In patient 1, although some characteristic features of Marshall–Smith syndrome such as everted lower lip, short nose and midface hypoplasia were observed, overall facial appearance, overgrowth features at 17 month of age, scoliosis, hypotonia and seizures were consistent with Sotos syndrome. Similarly, in patient 2, the facial appearance, tall stature and macrocephaly were consistent with Sotos syndrome. In both patients, their body weights were relatively low in comparison with their heights. This is consistent with the fact that, throughout childhood and early adolescence, the height was usually more significantly increased than weight in Sotos patients.[15] In addition, our patients did not show respiratory difficulties, one of specific features in Marshall–Smith syndrome, which cause early death in the neonatal period or early infancy.[7] Thus missense mutations in the DNA-binding/dimerization domain, which may lead to loss of transcriptional regulation by NFIX protein, could cause Sotos-like syndrome in two patients.

Many clinical features including tall statue, mental retardation, speech delay and high forehead are shared between our patients and three patients reported by Malan *et al.*[6] with *NFIX* abnormalities. The recognizable difference is autistic traits. Autistic traits are not observed in our patients but all of Malan *et al.*'s[6] patients. Thus there is a possibility that autistic traits are caused by haploinsufficiency of *NFIX* in Malan *et al.*'s[6] patients, but not by misssense mutations in the DNA-binding/dimerization domain. However, identification of a greater number of cases with *NFIX* mutations is required to confirm this hypothesis.

In conclusion, our report provides further evidences that *NFIX* is a causative gene for Sotos-like features. Abnormalities of *NSD1* are found in majority of Sotos syndrome cases and aberration of other genes including *NFIX* may be found in the minority of Sotos syndrome/Sotos-like features. Genetic testing of *NFIX* should be considered in such patients if no *NSD1* abnormalities were identified.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We thank the patients and their family members for their participation in this study. This work was supported by Research Grants from the Ministry of Health, Labour and Welfare (HS, N Miyake and N Matsumoto) and the Japan Science and Technology Agency (N Matsumoto), a Grant-in-Aid for Young Scientist from the Japan Society for the Promotion of Science (HS, HD and N Miyake) and a Grant-in-Aid for Scientific Research from Japan Society for the Promotion of Science (N Matsumoto).

1 Leventopoulos, G., Kitsiou-Tzeli, S., Kritikos, K., Psoni, S., Mavrou, A., Kanavakis, E. *et al.* A clinical study of Sotos syndrome patients with review of the literature. *Pediatr. Neurol.* **40,** 357–364 (2009).
2 Kurotaki, N., Imaizumi, K., Harada, N., Masuno, M., Kondoh, T., Nagai, T. *et al.* Haploinsufficiency of *NSD1* causes Sotos syndrome. *Nat. Genet.* **30,** 365–366 (2002).
3 Rayasam, G. V., Wendling, O., Angrand, P. O., Mark, M., Niederreither, K., Song, L. *et al. NSD1* is essential for early post-implantation development and has a catalytically active SET domain. *EMBO J.* **22,** 3153–3163 (2003).
4 Visser, R. & Matsumoto, N. in *Inborn Errors of Development* (eds Epstein, C. J., Erickson, R. P., Wynshaw-Boris, A.) 1032–1037 (Oxford University Press, New York, 2008).
5 Tatton-Brown, K. & Rahman, N. Sotos syndrome. *Eur. J. Hum. Genet.* **15,** 264–271 (2007).
6 Malan, V., Rajan, D., Thomas, S., Shaw, A. C., Louis Dit Picard, H., Layet, V. *et al.* Distinct effects of allelic *NFIX* mutations on nonsense-mediated mRNA decay engender either a Sotos-like or a Marshall-Smith syndrome. *Am. J. Hum. Genet.* **87,** 189–198 (2010).
7 Adam, M. P., Hennekam, R. C., Keppen, L. D., Bull, M. J., Clericuzio, C. L., Burke, L. W. *et al.* Marshall-Smith syndrome: natural history and evidence of an osteochondrodysplasia with connective tissue abnormalities. *Am. J. Med. Genet. A.* **137,** 117–124 (2005).
8 Saitsu, H., Kato, M., Mizuguchi, T., Hamada, K., Osaka, H., Tohyama, J. *et al. De novo* mutations in the gene encoding STXBP1 (MUNC18-1) cause early infantile epileptic encephalopathy. *Nat. Genet.* **40,** 782–788 (2008).
9 Gronostajski, R. M. Roles of the NFI/CTF gene family in transcription and development. *Gene* **249,** 31–45 (2000).
10 Kruse, U. & Sippel, A. E. Transcription factor nuclear factor I proteins form stable homo- and heterodimers. *FEBS Lett.* **348,** 46–50 (1994).
11 Armentero, M. T., Horwitz, M. & Mermod, N. Targeting of DNA polymerase to the adenovirus origin of DNA replication by interaction with nuclear factor I. *Proc. Natl. Acad. Sci. USA* **91,** 11537–11541 (1994).
12 Stefancsik, R. & Sarkar, S. Relationship between the DNA binding domains of SMAD and NFI/CTF transcription factors defines a new superfamily of genes. *DNA Seq.* **14,** 233–239 (2003).
13 MacArthur, M. W. & Thornton, J. M. Influence of proline residues on protein conformation. *J. Mol. Biol.* **218,** 397–412 (1991).
14 Shaw, A. C., van Balkom, I. D., Bauer, M., Cole, T. R., Delrue, M. A., Van Haeringen, A. *et al.* Phenotype and natural history in Marshall-Smith syndrome. *Am. J. Med. Genet. A* **152A,** 2714–2726 (2010).
15 Cole, T. R. & Hughes, H. E. Sotos syndrome: a study of the diagnostic criteria and natural history. *J. Med. Genet.* **31,** 20–32 (1994).

Supplementary Information accompanies the paper on Journal of Human Genetics website (http://www.nature.com/jhg)

CLINICAL REPORT

AMERICAN JOURNAL OF medical genetics PART A

Co-Occurrence of Prader–Willi and Sotos Syndromes

Nobuhiko Okamoto,[1]* Noriko Akimaru,[1] Keiko Matsuda,[1] Yasuhiro Suzuki,[2] Keiko Shimojima,[3] and Toshiyuki Yamamoto[3]

[1]Department of Medical Genetics, Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka, Japan

[2]Department of Pediatric Neurology, Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka, Japan

[3]Tokyo Women's Medical University Institute for Integrated Medical Sciences (TIIMS), Tokyo, Japan

Received 13 January 2010; Accepted 5 May 2010

A patient with atypical phenotypes of Prader–Willi syndrome (PWS) was subjected to investigate genomic copy numbers by microarray-based comparative genomic hybridization analysis. Severe developmental delay, relative macrocephaly, protruding forehead, cardiac anomalies, and hydronephrosis were atypical for PWS. Concurrent deletions of 15q11-13 and 5q35 regions were revealed and identified as paternally derived. The sizes and locations of the two deletions were typical for both deletions. Although each deletion independently contributed to the clinical features, developmental disturbance was very severe, suggesting combined effects. This is the first report of co-occurrence of PWS and STS. The co-occurrence of two syndromes is likely incidental. © 2010 Wiley-Liss, Inc.

Key words: Prader–Willi syndrome; Sotos syndrome; aCGH

How to Cite this Article:
Okamoto N, Akimaru N, Matsuda K, Suzuki Y, Shimojima K, Yamamoto T. 2010. Co-occurrence of Prader–Willi and Sotos syndromes.
Am J Med Genet Part A 152A:2103–2109.

INTRODUCTION

Prader–Willi syndrome (PWS; OMIM #176270) is caused by deficiency of paternally expressed imprinted transcripts within chromosome 15q11-q13 [Ledbetter et al., 1981]. It is characterized by obesity, hypotonia, hypogonadism, and behavioral abnormalities [Holm et al., 1993]. Most paternal PWS deletions are bracketed by recurrent breakpoints (BP)1 or BP2 and BP3. Preturbed expression of genes including *SNURF–SNRPN* and multiple small nucleolar RNAs (*snoRNAs*) are associated with the clinical manifestations of PWS, but the specific contributions of individual genes are under investigation. Recent analysis revealed that deficiency of HBII-85 *snoRNAs* causes the key characteristics of the PWS phenotype, although some atypical features suggest that other genes in the region may make more subtle phenotypic contributions [Sahoo et al., 2008].

Sotos syndrome (STS; OMIM#117550) is an overgrowth syndrome characterized by pre- and postnatal overgrowth, macrocephaly, developmental delay, advanced bone age, and a distinctive face including frontal bossing, frontal sparseness of hair, hypertelorism, downslanting palpebral fissures, and pointed chin. Haploinsufficiency of the *NSD1* gene due to 5q35 microdeletions or intragenic mutations causes STS [Kurotaki et al., 2002]. Miyake et al. [2003] observed that microdeletions in STS are mostly of paternal origin. Common deletion breakpoints were located at two flanking low copy repeats (LCR), implying that non-allelic homologous recombination (NAHR) between LCRs is the major mechanism for the common deletion in STS [Kurotaki et al., 2005; Visser et al., 2005]. Central nervous system anomalies, cardiovascular and urogenital symptoms are more frequent in the microdeletion group [Nagai et al., 2003].

In this study, a patient with atypical phenotypes of PWS was subjected to investigate genomic copy numbers by microarray-based comparative genomic hybridization (aCGH) analysis. Concurrent deletions of 15q11-13 and 5q35 regions were detected and identified as paternally derived. Although each deletion independently contributed to the clinical features, growth and developmental disturbance were very severe, suggesting combined effects. This is the first report of co-occurrence of PWS and STS.

CLINICAL REPORT

A 14-year-old male propositus is the first-born child of healthy and non-consanguineous parents. After uncomplicated pregnancy, he was born at 39 weeks of gestation by induced delivery with overgrowth of length with 53 cm (90th centile).

Grant sponsor: Ministry of Health, Labour and Welfare in Japan.
*Correspondence to:
Dr. Nobuhiko Okamoto, Department of Medical Genetics, Osaka Medical Center and Research Institute for Maternal and Child Health, 840 Murodo-cho, Izumi, Osaka 594-1101, Japan. E-mail: okamoto@osaka.email.ne.jp
Published online 15 July 2010 in Wiley InterScience (www.interscience.wiley.com)
DOI 10.1002/ajmg.a.33544

His birth weight was within a normal limit as 3,010 g (25th centile). He was the first child of a 26-year-old mother and a 30-year -old father. Since cardiac murmur was found at birth, he was transferred to the neonatal intensive care unit and ventricular septal defect (VSD), atrial septal defect (ASD), and patent ductus arteriosus (PDA) were revealed by echocardiography. Micropenis and bilateral cryptorchidism were noticed. He had severe hypotonia and feeding difficulties in the early infantile period. Until his sucking improved at 6 months old, nasal tube feeding was required. Ultrasonography revealed bilateral vesicoureteral reflux and hydronephrosis. He showed a severe developmental delay with head control at 1 year of age and sitting alone at 6 years of age. He had generalized seizures at age 6 years. Electroencephalography revealed sporadic spikes at that time. Brain MRI showed no significant findings. He developed progressive obesity, as his weight was 10.0 kg (75th centile) at 9 months old of age and 12.4 kg (95th centile) at 1 year old of age. Conventional G-band chromosome analysis showed a normal male karyotype, and subsequent conventional FISH analysis for *SNRPN* revealed a deletion, indicating a diagnosis of PWS. In spite of that, relative macrocephaly, protruding forehead, frontal baldness, and mild overgrowth were atypical for phenotypic features of PWS (Fig. 1A). Although he was interested in food, hyperphagia was not prominent because of his restricted locomotive abilities. Gradually, his height SD scores decreased (Fig. 2). Partial growth hormone deficiency was found by endocrinological studies. When he was 14 years of age his bone age was measured at the 11-year-old level. His parents did not choose GH replacement therapy.

When we examined the patient at the age of 14 years, he showed severe mental retardation without vocalized words, muscular hypotonia, hypopigmentation, scoliosis, and distinctive facial features including protruding forehead; strabismus; hypertelorism; downslanting palpebral fissures; epicanthal folds; full cheeks; microstomia with downturned corners of the mouth; small hands with tapering fingers; and small feet (Fig. 1B). A wheel chair was required for him because his hip joint was unstable and he could not stand alone. His intelligent quotient (IQ) was measured by Kyoto Scale of Psychological Development as below 10. He was a calm and friendly boy. His interest in food became obvious, but self-injurious behaviors such as skin picking were not observed. Behavioral problems associated with STS including autistic spectrum disorder, hyperactivity, and aggression were not present. His weight was 29 kg (<3rd centile), and his length was 132 cm (<3rd centile) (Fig. 2). His head circumference was mean for his age. A comparison of typical features of PWS and STS and their clinical presentation in the patient are shown (Table I).

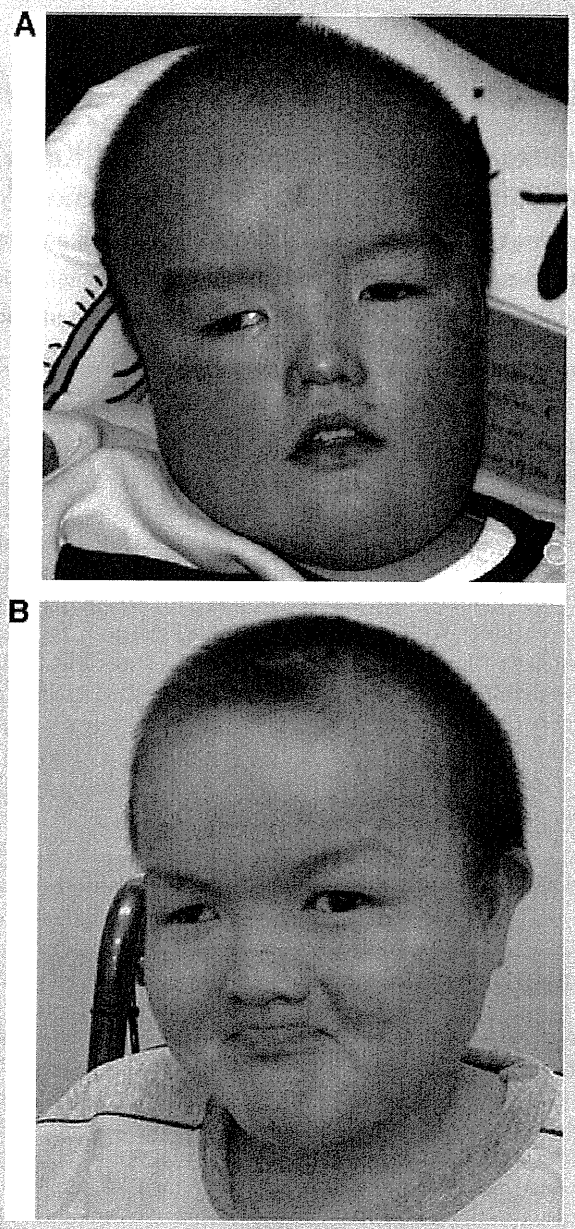

FIG. 1. Facial appearance of the patient at 6 years old (A) and 14 years old (B).

MATERIALS AND METHODS

After obtaining informed consents based on a permission approved by the institution's ethical committee, peripheral blood samples were obtained from the patient and his parents. Genomic DNAs were extracted using the QIAquick DNA extraction kit (QIAgen, Valencia, CA).

Based on the hypothesis that the patient might have an atypically larger deletion of chromosome 15 or have additional chromosomal aberrations, aCGH analysis was performed using the Human Genome CGH Microarray 60K (Agilent Technologies, Santa Clara, CA) as described previously [Shimojima et al., 2009].

Metaphase nuclei were prepared from peripheral blood lymphocytes by mean of standard methods and used for FISH analysis with human BAC clones selected from the UCSC genome browser (http://www.genome.ucsc.edu) as described elsewhere [Shimojima et al., 2009]. Physical positions refer to the March 2006 human reference sequence (NCBI Build 36.1).

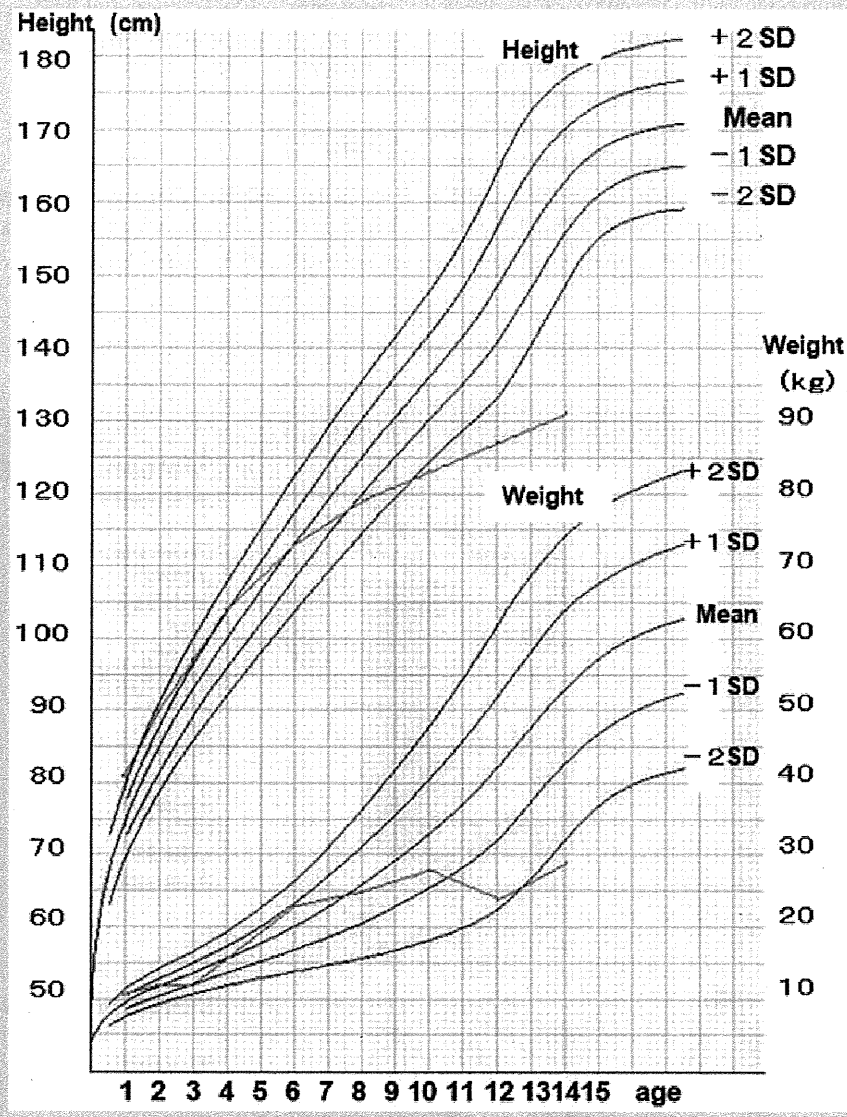

FIG. 2. Growth curve of the patient. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE I. A Comparison of Typical Features of PWS and STS and Their Clinical Presentation in the Current Patient

	Prader–Willi	Sotos	Current patient
Hypotonia	+	+	++
Mental delay	+	+	++
Hypopigmentation	+	−	+
Prominent forehead	−	+	+
Strabismus	+	+	++
Over growth	−	+	−
Growth delay	+	−	++
Obesity	+	−	+
Epilepsy	−	+	+
Congenital heart disease	−	+	+
Scoliosis	+	+	++
Hydronephrosis	−	+	+
Hypogonadism	+	−	+

+, common features; ++, prominent manifestations.