2009.

３．学会発表

1．Tomita H, Tanaka C, Kim HB, Bunney WE. Microarray gene expression profiles in neuronal and glial cell lines after lithium treatment. Society for Neuroscience 37th annual meeting, San Diego CA., USA. November 3-7, 2007

2. Tomita H. The importance of quality control in brain bank management. Symposium "Toward constructing brain bank of psychiatric diseases". World Federation of Societies of Biological Psychiatry 2nd Asia-Pacific Congress, Toyama, Japan. September 11-13, 2008.

3. Tomita H. Psychoneuroimmunology in schizophrenia. Symposium "Recent advances and future directions in psychoneuroimmunology as useful approaches to psychiatric disorders" World Federation of Societies of Biological Psychiatry 2nd Asia-Pacific Congress, Toyama, Japan. September 11-13, 2008.

4. Tomita H. Effect of mood stabilizers on genome-wide gene expression profiles of human CNS-derived cell lines. Symposium "Genome-wide studies of bipolar disorder and mood stabilizaion". World Congress of Psychiatric Genetics 15th annual meeting, Osaka, Japan. October 11-15, 2008

5. Tomita H, Tanaka C, Kim HB, Bunney WE. Neuron- and glia- specific gene expression profiles after lithium treatment. Collegium internationale neuro-psychopharmacologicum 50th congress, Munich, Germany. July 13-17, 2008

6. Tanaka C, Ishikawa M, Tomita H. Hypoxia-induced gene expression profiles of Neuron and Oligodendrocyte. Collegium internationale neuro-psychopharmacologicum 50th congress, Munich, Germany. July 13-17, 2008

7. Yu Z, Tanaka C, Komatsu H, Takahashi S, Kim HB, Kimura K, Sora I, Bunney WE, Tomita H. Microarray gene expression profiles in neuronal and glial cell lines after lithium, valproate, carbamazepine and lamotrigine treatment. World Federation of Societies of Biological Psychiatry 2nd Asia-Pacific Congress, Toyama, Japan. September 11-13, 2008.

8. Tomita H, Tanaka C, Yu Z. FACS-array approach into immunological aspects of schizophrenia. World Congress of Psychiatric Genetics 15th annual meeting, Osaka, Japan. October 11-15, 2008

9. Komatsu H, Tanaka C, Yu Z, Kimura K, Takahashi S, Sora I, Matsuoka H, Tomita H. Expression profiles of BDNF transcript variants in neuronal and glial cell lines after treatment with mood stabilizers. World Congress of Psychiatric Genetics 15th annual meeting, Osaka, Japan. October 11-15, 2008

10. Tomita H, Tanaka C, Yu Z, Kimura K, Bunney WE. Hypoxia-induced gene expression profiling in neuron and oligodendrocyte. Society for Neuroscience 38th annual meeting, Washington DC, USA. November 15-19, 2008

11. Itoi K, Nakamura H, Yokokawa T, Sato Y, Kobayashi K, Tanaka C, Tomita H, Uchida K, Iwasaki Y, Ishii Y. A comprehensive gene expression analysis of the locus coeruleus noradernergic neurons during early development by the FACS-array technology. Society for Neuroscience 38th annual meeting, Washington DC, USA. November 15-19, 2008

12. Tanaka C, Yu Z, Kimura K, Ishii N, Tomita H. Microarray gene expression profiling of Th1/Th2 helper t cells as a tool for neuropsychoimmunology. Society for Neuroscience 38th annual meeting, Washington DC, USA. November 15-19, 2008

Ｈ．知的財産権の出願・登録状況（予定を含む。）

1）特許取得：

1．United States Patent Application 7,022,480

Akil; Huda; Bunney, JR.; William E.; Choudary; Prabhakara V.; Evans; Simon J.; Jones; Edward G.; Li; Jun; Lopez; Juan F.; Thompson; Robert C.; Myers; Richard; Tomita; Hiroaki; Vawter; Marquis P; Watson; Stanley "FGF2-related methods for diagnosing and treating depression" (Date of Filing: January 15, 2009)

2. United States Patent Application 20090117565
Akil; Huda; Bunney, JR.; William E.; Choudary; Prabhakara V.; Evans; Simon J.; Jones; Edward G.; Li; Jun; Lopez; Juan F.; Thompson; Robert C.; Myers; Richard; Tomita; Hiroaki; Vawter; Marquis P; Watson; Stanley "Compositions and methods for diagnosis and treating mood disorders"(Date of Filing: May 7, 2009)

2) 実用新案登録: なし

3) その他: なし

Akil; Huda; Bunney, JR.; William E.; Choudary; Prabhakara V.; Evans; Simon J.; Jones; Edward G.; Li; Jun; Lopez; Juan F.; Thompson; Robert C.; Myers; Richard; Tomita; Hiroaki; Vawter; Marquis P; Watson; Stanley "FGF2-related methods for diagnosing and treating depression" (Date of Filing: January 15, 2009)

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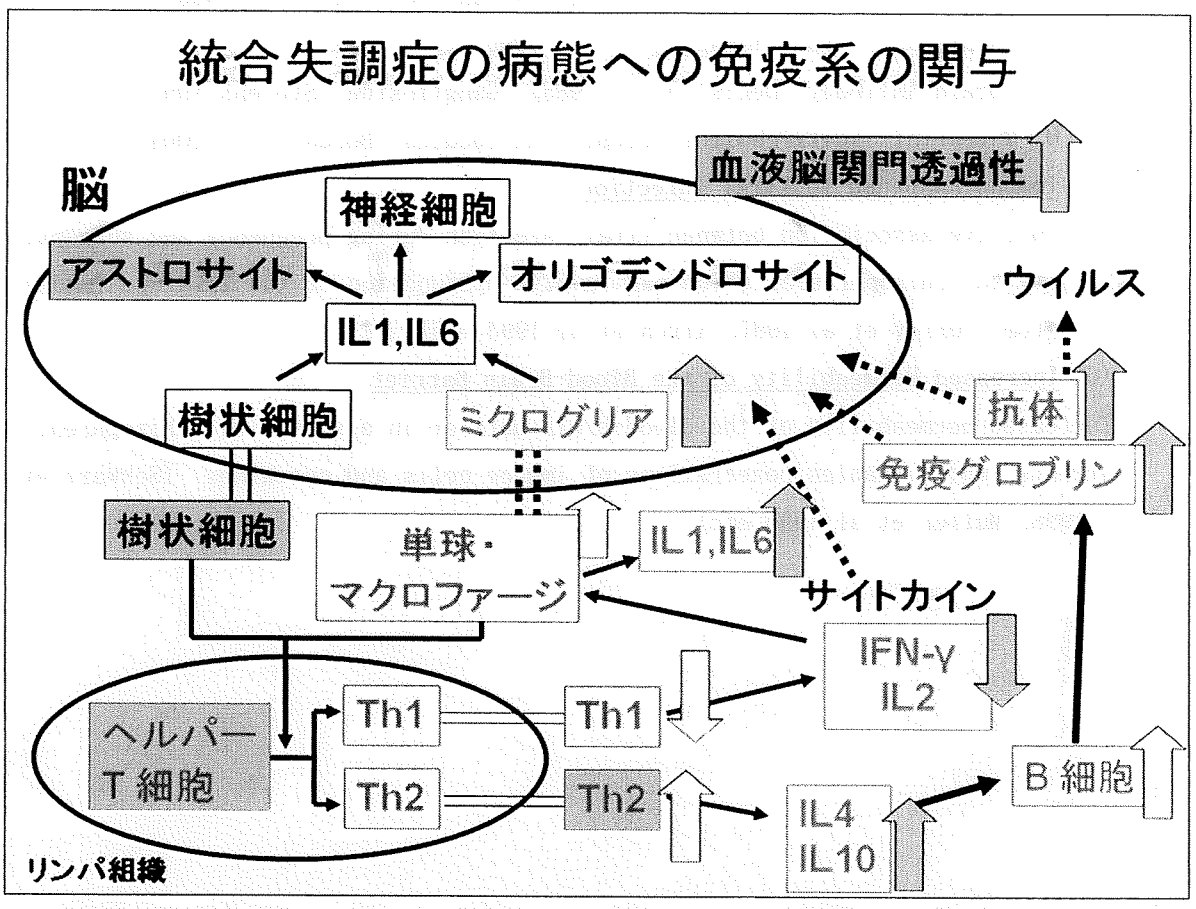
2) 実用新案登録：なし

3) その他：なし

資　　料

（資料１：統合失調症への免疫系の関与）



統合失調症への免疫系の関与を示す証拠に下記の相互に関連する現象があげられる。

(1) Activated Microglia

Activated microglia in a subset of schizophrenic patients based on postmortem studies (Kreutzberg et al 1996 etc)

(2) Imbalanced Subpopulation of Helper T Cell

A shift from Th1 to Th-2 helper T cell-immune reactivity in schizophrenic patients, especially with predominant negative symptom and/or poor therapy outcome, based on measurements of Th1- and Th2-relevant cytokines (Schwarz et al 2001 etc)

(3) Increased Immunoglobulins

Increased serum Immunoglobulin E and cerebral spinal fluid Immunoglobulin G in schizophrenic patients with predominant negative symptom and/or poor therapy outcome

(4) Frequent Detection of Antibodies against Viruses and Brain Structures in schizophrenic sera or cerebrospinal fluid

Herpes Simplex Virus (Bartova et al 1987 etc), Cytomegalovirus

(Torrey et al 1978 etc), Epstein Barr Virus (De Lisi et al 1986 etc),
Borna Disease Virus (Yamaguchi et al 1999 etc)
Antibrain Antibody (DeLisi et al 1985), Ganglioside (Stevens 1992)
M1 Muscarinic acetylcholine receptor antibodies (Borda et al 2004)

(5) Immune Response to Viral Infection

Positive association between viral infection during pregnancy and susceptibility to schizophrenia, which can involve dysfunction of the immature immune system (Torrey et al 1997, Kirch et al 1993 etc)

(6) Increased Permeability of the Blood-Brain Barrier

Increased permeability of the blood-brain barrier in a subset of schizophrenic patients, which enables penetrations of immune cells and cytokines (Schwarz et al 1998, Muller et al 1995 etc)

（資料２：臨床情報一般）

匿名化ID：　　性別：　　年齢：

診断名：

家族歴：何人兄弟の何番目：

精神疾患罹患者（診断名・関係）：

既往歴・合併症（診断名・発症年齢）：

アレルギー：

生育歴：

教育歴（最終学歴）：

職歴：

婚姻歴：

発症年齢：

初発症状：

病歴：

入院回数・期間（何回・何ヶ月）：

治療歴・抗精神病薬（一般名・最大容量・期間・効果）：

気分安定薬（一般名・最大容量・期間）：

抗パーキンソン薬（一般名・最大容量・期間）：

抗ヒスタミン剤（一般名・最大容量・期間）：

副作用・EPS：　　肥満：　　多飲水：

その他：

（資料３：Th1ヘルパーT細胞マーカーの文献考察の要約）

Th1　マーカー：CD4およびCXCR3

Ref No	マーカー	抗体	抗体メーカー	FCM機器	論文名	last	
H2	CXCR3	FITC-anti CXCR3	Dako	FACScan:BD	Cancer Sci	Kazunari Tanabe *Tokyo Women's Medical University*	2006 (97) 8, 780–786
	CCR5	FITC-anti CCR5	PharMingen				
	CD4	PE-antiCD4	BD				
H4	CXCR3	PE-antiCXCR3	R&D Systems	FACStar ; BD	J. Immunol	Seishi Kyoizumi *Department of Radiobiology, Radiation Effects Research Foundation*	2002(169) 39–48.
H7	CD4	FITC-antiCD4	BD	FACSCoulter	Ann Rheum Dis	P M VilligerRheumatology and Clinical Immunology and Allergology, University Hospital, CH-3010 Bern, Switzerland	2005(64)318-320
	CXCR3	APC-antiCXCR3					
H9;Tissue	CXCR3	PE/FITC- antiCXCR3	Pharmingen	FACSCalibur;BD	Int. J. Cancer	Iwao Sasaki *Tohoku University School of Medicine*	2005(116) 949–956
	CCR5	PE-antiCCR5					
H33	CD4	FITC/Cy-chrome-antiCD4	BD	FACSCalibur ;BD	American Journal of Gastroenterology	Sheung Tat Fan *The university of Hong Kong*	20041111-1121
	CCR5	Phycoerythrin-antiCCR5					
	CXCR3	Phycoerythrin-antiCXCR3					
H12	CXCR3	FITC/NHS-LC-Biotin-antiCXCR3	Boehringer Mannheim Corp/Pierce	FACScan;BD	Eur. J. Immunol.	Christina M. Parker*Brigham and Women's Hospital and Harvard Medical School,* Harvard Medical School	2000(30) 819–826
	CCR5	FITC/NHS-LC-Biotin-antiCCR5					
H10**	CD4	anti-CD4-APC	Beckman	FACSCalibur	Eur. J. Immunol.	Federica Sallusto *Institute for Research in Biomedicine,*	2003(33)474–482
	CCR5	anti-CCR5	PharMingen				
	CXCR6	anti-CXCR6	Millennium Pharmaceuticals				
	CXCR3	anti-CXCR3					
	**検出は2次抗体を用いた。						
H11	CD4	PerCP-antiCD4	BD	FACScan;BD	Journal of Clinical Immunology	KAZUHIKO TAKEHARA *Kanazawa University Graduate School of Medical*	2003(23),4
	CXCR3	PE-antiCXCR3	BD				
H14	CD4	PerCP-antiCD4	BD	FACSCalibur; BD	Investigative Ophthalmology & Visual Science	Andrew D. Dick *University of Bristol*	2004(45)1,170-176
	CCR5	PE-antiCCR5	BD				
	CXCR3	PE-antiCXCR3	BD				
H15	CD4	PE-anti-CD4	PharMingen	FACScan;BD	J. Clin. Invest.	Charles R. Mackay *LeukoSite, Inc.,*	1998(101),4, 746–754
	CXCR3	biotinylated anti-CXCR3 mAb	自作				
	CCR5	anti-CCR5	自作				
H16	CD4	(PE)-labeled anti-human CD4	PharMingen	FACScan ; BD	Mod Rheumatol	Saburo Sone *Tokushima University*	2003 (13)114–120
	CXCR3	FITC-labeled antihuman CXCR3					
H19	CXCR3	FITC-antiCXCR3	DAKO	FACScan;BD	Acta Med. Okayama	Hirofumi Makinoa *Okayama University Graduate School of Medicine ,*	2006(60)3,149-157
	CCR4	FITC-antiCCR4 mAb	KyowaHakko				
	CD4	Per-CP-antiCD4	BD				

（資料４：Th2ヘルパーT細胞マーカーの文献考察の要約）

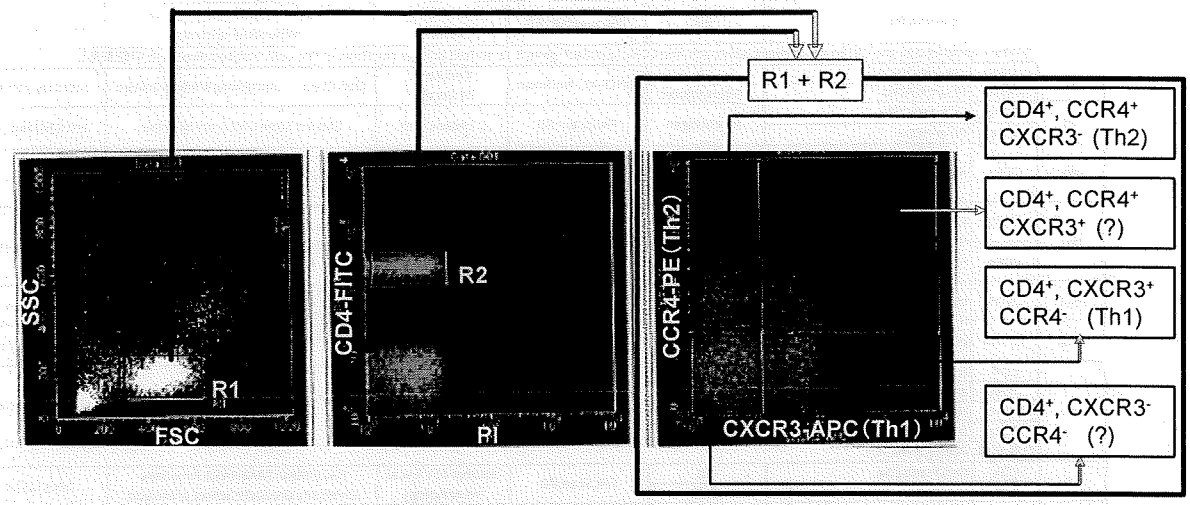
Th2

マーカー：CD4およびCCR4?

Ref No	マーカー	抗体	抗体メーカー	FCM機器	論文名	last	
H4	CRTH2	PE indirectly labeled CRTH2 (with biotinylation followed by PE-streptavidin)	分譲Dr. K. Nagata (BML,).	FACStar ; BD	J. Immunol	Seishi Kyoizumi *Department of Radiobiology, Radiation Effects Research Foundation*	2002(169)39-48.
H3*	CCR4	PE-antiCCR4	BD	FACSCalibur ;BD	Immunology Letters	Namit Ghildyal *Department of Immunotherapeutics*	102 (2006) 110–114
*[When compared to the CRTh2 enrichment approach, the CCR4 approach gave 8- to 10-fold greater numbers of Th2 cells isolated directly]との記載あり							
H1	CD4	Cy5-antiCD4	EB	EPICS-XL ; Beckman	Cellular & Molecular	Qun Chen *Guangdong Medical College*	2005(2)5,387-392
	CRTH2	PE-antiCRTH2	Miltenyibiotec				
H5	CCR4	FITC-antiCCR4	PharMingen	FACScan ;BD	J. Leukoc. Biol.	Saburo Sone *University of Tokyo*	2001(70)749-755
	CD4	PE-antiCD4					
H6	CCR4	mouseIgG-antiCCR4	自作	FACSVantage /Calibar (BD)	Am J Pathol	James J. Campbell *Institute for Lung Health, Leicester University Medical School*	2002(160)347–355
H12	CCR3	FITC/NHS-LC-Biotin-antiCCR3	Boehringer Mannheim Corp/Pierce	FACScan;BD	Eur. J. Immunol.	Christina M. Parker*Brigham and Women's Hospital and Harvard Medical School,* Harvard Medical School	2000(30) 819–826
	CCR4	FITC/NHS-LC-Biotin-antiCCR4					
H28	CRTH2	biotin-antiCRTH2	自作	FACSCalibur	Clin Exp Immunol	S. SAITO *Toyama Medical and Pharmaceutical University,*	2001(123)105-111
H29	CRTH2	biotin-antiCRTH3	自作	FACSCalibur	FEBS Letters	Shoichi Takanoa *BioMedical Laboratories, Inc*	1999 (459) 195-199
H10	CD4	anti-CD4-APC	Beckman	FACSCalibur	Eur. J. Immunol.	Federica Sallusto *Institute for Research in Biomedicine,*	2003(33)474–482
	CCR4	anti-CCR4	PharMingen				
	CRTH2	anti-CRTh2	自作				
	CCR3	anti-CCR3	Millennium Pharmaceuticals				
**検出は2次抗体を用いた。							
H11	CD4	PerCP-antiCD4	BD	FACScan;BD	Journal of Clinical Immunology	KAZUHIKO TAKEHARA *Kanazawa University Graduate School of Medical*	2003 (23),4
	CCR4	anti-CCR4	自作				
H14	CD4	PerCP-antiCD4	BD	FACSCalibur; BD	Investigative Ophthalmology & Visual Science	Andrew D. Dick *University of Bristol*	2004(45)1,170-176
	CCR4	PE-antiCCR4	BD				
H16	CD4	PE- anti CD4	PharMingen	FACScan ; BD	Mod Rheumatol	Saburo Sone *Tokushima University*	2003 (13)114–120
	CCR4	FITC-antiCCR4					
H18	CD4	chlorophyll protein–antiCD4	BD	FACSCalibur machine	J ALLERGY CLIN IMMUNOL	Clare M. Lloyd, PhD *United Kingdom*	2003(112)6,1155-1161
	CCR3	R-PE–antiCCR3	R&D Systems),				
	CCR4	R-PE–antiCCR4	BD				
	CCR8	Anti-CCR8 (pAb)	AMS Biotechnology,				

（資料５：細胞ソーティング法によるTh1およびTh2ヘルパーT細胞の選別）

FACSによるヘルパーT細胞　Th1⁺細胞およびTh2⁺細胞の選別 (4 Way Sorting)



① FSC、SCCによりリンパ球分画（R1)を選別
② PI、CD4-FITCによりPI陰性のCD4⁺ヘルパーリンパ球分画（R2)を選別
③ R1、R2を展開し、CXCR3-APC、CCR4-PEにより、4 Way Sorting
(1) PI陰性のCD4⁺, CXCR3⁺, CCR4⁻分画（Th1ヘルパーリンパ球細胞）
(2) PI陰性のCD4⁺, CCR4⁺, CXCR3⁻分画（Th2ヘルパーリンパ球細胞）
(3) PI陰性のCD4⁺, CCR4⁺, CXCR3⁺分画
(4) PI陰性のCD4⁺, CCR4⁻, CXCR3⁻分画

（資料６：細胞数の再現性実験）

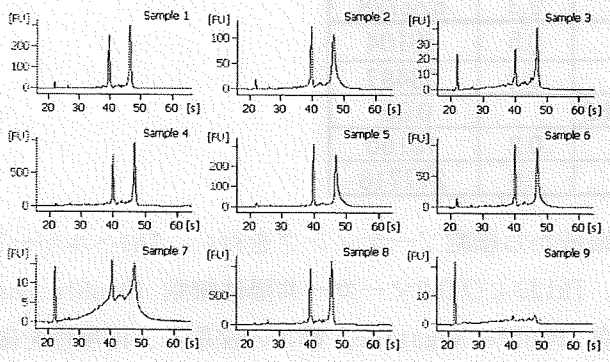
Sample	採血量 [mL]	リンパ球 [個]	分画	%cell	Sorting cell
健常者1-1	17	2.6×10^7	Th1	0.3	217300
			Th2	0.3	165073
			Th1/Th2		1.32
			WP	0.2	125522
			WN	0.9	521596
健常者1-2	13	3.4×10^7	Th1	0.9	267171
			Th2	0.6	207677
			Th1/Th2		1.29
			WP	0.4	131528
			WN	2.5	710538
健常者2-1	12	3.5×10^7	Th1	0.9	275834
			Th2	0.8	260448
			Th1/Th2		1.06
			WP	0.4	149658
			WN	4	1175080
健常者2-2	12.5	3.0×10^7	Th1	0.9	116011
			Th2	0.7	100212
			Th1/Th2		1.16
			WP	0.3	55079
			WN	3.7	609961
健常者3-1	10	3.5×10^7	Th1	0.3	89931
			Th2	0.3	90141
			Th1/Th2		1.00
			WP	0.1	44599
			WN	2.3	622728
健常者3-2	12	2.6×10^7	Th1	0.5	50104
			Th2	0.4	58497
			Th1/Th2		0.86
			WP	0.2	15160
			WN	2.8	277718

健常者３名から異なる採取日に採血した血液から細胞ソーティングを行い、Th1ヘルパーT細胞（Th1）、Th2ヘルパーT細胞（Th2）、Th1およびTh2マーカー共陽性細胞（Double Positive, WP）、Th1・Th2陰性ヘルパーT細胞（Double Negative, WN）の採取し、再現性を確認した。

（資料７：RNAの収量とクオリティーコントロール）

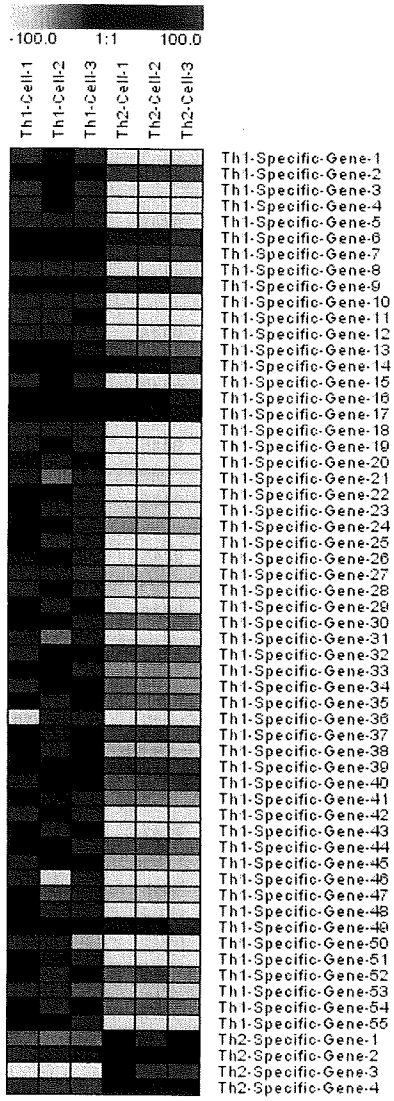
分画	Sample	採血量 [mL]	リンパ球 [個]	%cell	Sorting cell	totalRNA 溶出量[μL]	RNA Area	RNA濃度 (pg/μl)	rRNA比 [28S/18S]	RIN値
Th1	健常者1-1	17	2.6×10^7	0.3	217300	30	963.2	2559.6	1.5682	9.8 (B.02.02)
	健常者1-2	13	3.4×10^7	0.9	267171	30	1330.9	3536.5	1.8749	9.7 (B.02.02)
	健常者2-1	12	3.5×10^7	0.9	275834	30	742.8	2996.9	1.8654	9.6 (B.02.02)
	健常者2-2	12.5	3.0×10^7	0.9	116011	30	192.0	774.6	2.7857	8.1 (B.02.02)
	健常者3-1	10	3.5×10^7	0.3	89931	30	274.0	1674.8	1.0236	5.3 (B.02.02)
	健常者3-2	12	2.6×10^7	0.5	50104	30	274.0	1674.8	1.0236	5.3 (B.02.02)
Th2	健常者1-1	17	2.6×107	0.3	165073	30	737.8	1960.5	2.1725	9.3 (B.02.02)
	健常者1-2	13	3.4×107	0.6	207677	30	548.0	1456.2	1.6528	9.1 (B.02.02)
	健常者2-1	12	3.5×107	0.8	260448	30	688.9	2779.4	2.4421	10.0 (B.02.02)
	健常者2-2	12.5	3.0×107	0.7	100212	30	150.4	607.0	2.179	8.0 (B.02.02)
	健常者3-1	10	3.5×107	0.3	90141	30	227.4	1390.1	2.6666	9.2 (B.02.02)
	健常者3-2	12	2.6×107	0.4	58497	30	227.4	1390.1	2.6666	9.2 (B.02.02)
WN	健常者1-1	17	2.6×107	0.9	521596	30	3569.1	9484.1	1.518	9.4 (B.02.02)
	健常者1-2	13	3.4×107	2.5	710538	30	4408.8	11715.4	1.4489	9.2 (B.02.02)
	健常者2-1	12	3.5×107	4	1175080	30	7782.1	31398.2	1.991	9.8 (B.02.02)
	健常者2-2	12.5	3.0×107	3.7	609961	30	2327.7	9391.6	2.1019	9.8 (B.02.02)
	健常者3-1	10	3.5×107	2.3	622728	30	812.8	4969.0	0.2213	8.0 (B.02.02)
	健常者3-2	12	2.6×107	2.8	277718	30	812.8	4969.0	0.2213	8.0 (B.02.02)
WP	健常者1-1	17	2.6×107	0.2	125522	30	255.6	679.2	2.0105	8.0 (B.02.02)
	健常者1-2	13	3.4×107	0.4	131528	30	279.1	741.6	1.6428	7.3 (B.02.02)
	健常者2-1	12	3.5×107	0.4	149658	30	235.9	951.8	2.3477	10.0 (B.02.02)
	健常者2-2	12.5	3.0×107	0.3	55079	30	41.6	167.7	2.3923	6.6 (B.02.02)
	健常者3-1	10	3.5×107	0.1	44599	30	13.5	82.6	1.7426	7.5 (B.02.02)
	健常者3-2	12	2.6×107	0.2	15160	30	13.5	82.6	1.7426	7.5 (B.02.02)

Agilent BioAnalyzer 2100 泳動パターン（代表サンプル）



健常者３名から細胞ソーティングにより回収した、Th1ヘルパーT細胞（Th1）、Th2ヘルパーT細胞（Th2）、Th1およびTh2マーカー共陽性細胞（Double Positive, WP）、Th1・Th2陰性ヘルパーT細胞（Double Negative, WN）から総RNAを抽出し、総RNAのクオリティー・コントロールを行った。Agilent BioAnalyzer 2100にAgilent RNA Picoキットを用いて総RNAサンプルの泳動実験を行い、リボソームRNAの18Sと28Sの比（28S/18S比）やRIN(RNA Integrity Number)等の総RNAのクオリティー・コントロールの指標を確認した。総じて28S/18S比は1.5以上、RIN値は8以上あることが確認でき、総RNAの質は良好であることが確認された。28S/18S比1.5未満、RIN値7未満の検体は以降の実験には使用しない。

（資料８：マイクロアレイ解析による新規Th1細胞・Th2細胞特異的遺伝子群の特定）



（資料８：Th1ヘルパーT細胞遺伝子発現プロファイル）

Gene Category	List Hits	List Total	Population Hits	Population Total	EASE score
response to biotic stimulus	35	182	755	9445	0.000002
defense response	31	182	698	9445	0.0000219
immune response	28	182	628	9445	0.0000593
response to pest/pathogen/parasite	21	182	393	9445	0.0000615
response to stress	26	182	689	9445	0.00144
antigen presentation	5	182	28	9445	0.00186
response to external stimulus	38	182	1209	9445	0.00236
antigen presentation, exogenous antigen	4	182	15	9445	0.00266
antigen processing, exogenous antigen via MHC class II	4	182	15	9445	0.00266
cytokine binding	6	187	53	9638	0.00344
MHC class II receptor activity	4	187	17	9638	0.00394
catabolism	25	182	734	9445	0.00676
cell proliferation	28	182	900	9445	0.0124
cytoplasm	84	180	3578	9342	0.0159
antigen processing	4	182	28	9445	0.0159
intracellular	124	180	5701	9342	0.019
cell death	14	182	360	9445	0.0209

（資料９：Th2ヘルパーT細胞遺伝子発現プロファイル）

Gene Category	List Hits	List Total	Population Hits	Population Total	EASE score
cell death	13	128	360	9445	0.00326
death	13	128	364	9445	0.00357
RNA binding	13	131	380	9638	0.00517
apoptosis	12	128	335	9445	0.00538
programmed cell death	12	128	336	9445	0.0055
regulation of apoptosis	8	128	185	9445	0.0123
isomerase activity	5	131	91	9638	0.0344
mRNA splicing	3	128	22	9445	0.0348
intramolecular isomerase activity	3	131	24	9638	0.0411

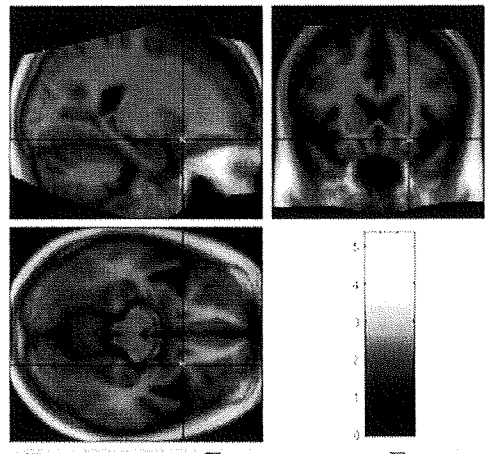
（資料１０）

統合失調症罹患者群と健常対照者群の脳体積の比較

［全脳体積］　灰白質、白質とも、頭蓋内体積で割ることで、個人の頭蓋内体積の差異を補正し、Gray Matter Ratio、White Matter Ratioとして計測。年齢、性を補正した上で、健常群と疾患群をANCOVAにて解析。

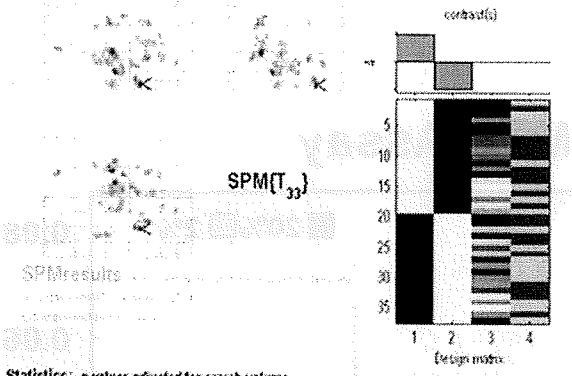
Gray Matter Ratio:　t = 1.711　（ df = 33 ）　P=0.096
White Matter Ratio: t = -1.345　（ df = 33 ）　P=0.188

［局所脳体積］　右下前頭回白質の体積（閾値：FWE p<0.05）



（資料１１）

統合失調症罹患者群と健常対照者群の白質繊維束統合性の比較



FEW p<0.05で有意差のある領域

- 左上側頭回
- 左海馬
- 右側頭極

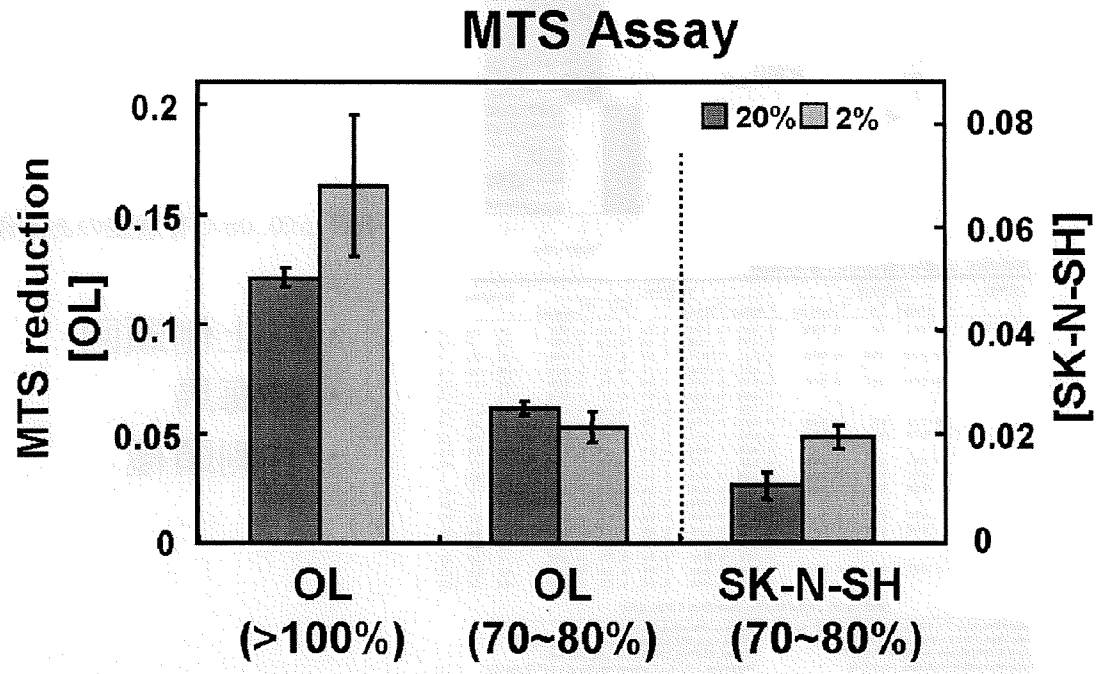
Statistics: *p-values adjusted for search volume*

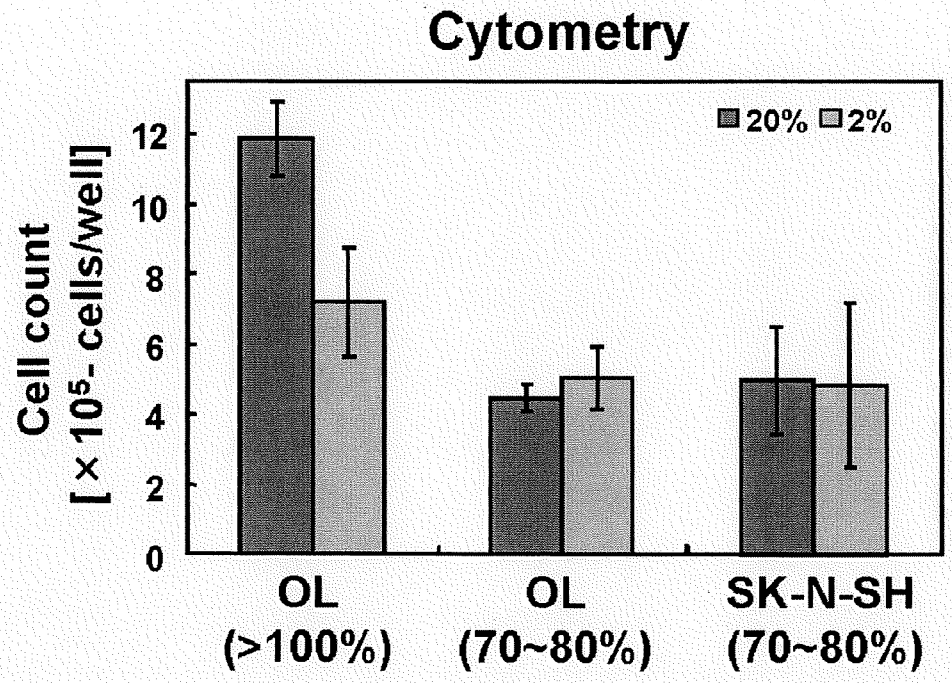
set-level		cluster-level		voxel-level					mm mm mm
p	c	$p_{corrected}$	k_E	$p_{uncorrected}$	$p_{FWE-corr}$	$p_{FDR-corr}$	T	Z_E	$p_{uncorrected}$			
0.00050	0.003	50	0.001	0.005	0.006	6.54	5.20	0.000	26	24	-36
				0.007	0.006	5.40	4.54	0.000	34	6	-32
	0.000	156	0.000	0.022	0.006	5.08	4.39	0.000	-28	-20	0
				0.128	0.006	5.23	4.42	0.000	-40	-16	-8
	0.000	162	0.000	0.033	0.006	5.01	4.29	0.000	-16	-16	-22
				0.154	0.006	5.07	4.33	0.000	-8	-8	-24
				0.233	0.006	4.71	4.07	0.000	-12	-22	-12
	0.623	48	0.003	0.095	0.006	5.35	4.51	0.000	26	20	-8
	0.008	64	0.004	0.102	0.006	5.33	4.50	0.000	-34	-24	32
				0.428	0.006	4.65	4.03	0.000	-24	-14	20
	0.193	18	0.088	0.118	0.006	5.27	4.46	0.000	-26	-6	40
	0.672	31	0.031	0.137	0.006	5.20	4.42	0.000	-26	-52	2
	0.015	55	0.006	0.158	0.006	5.14	4.37	0.000	-10	6	-16
				0.751	0.008	4.25	3.77	0.000	-16	0	-18
	0.178	19	0.081	0.175	0.006	5.09	4.34	0.000	-28	22	32
	0.000	202	0.000	0.189	0.006	5.06	4.32	0.000	14	-14	-24
				0.212	0.006	5.01	4.29	0.000	-6	-18	-2
				0.221	0.008	4.98	4.27	0.000	8	-10	-18
	0.005	74	0.002	0.194	0.006	5.05	4.31	0.000	42	-26	-12
				0.287	0.008	4.86	4.19	0.000	44	-36	-10

table shows 3 local maxima more than 8.0mm apart

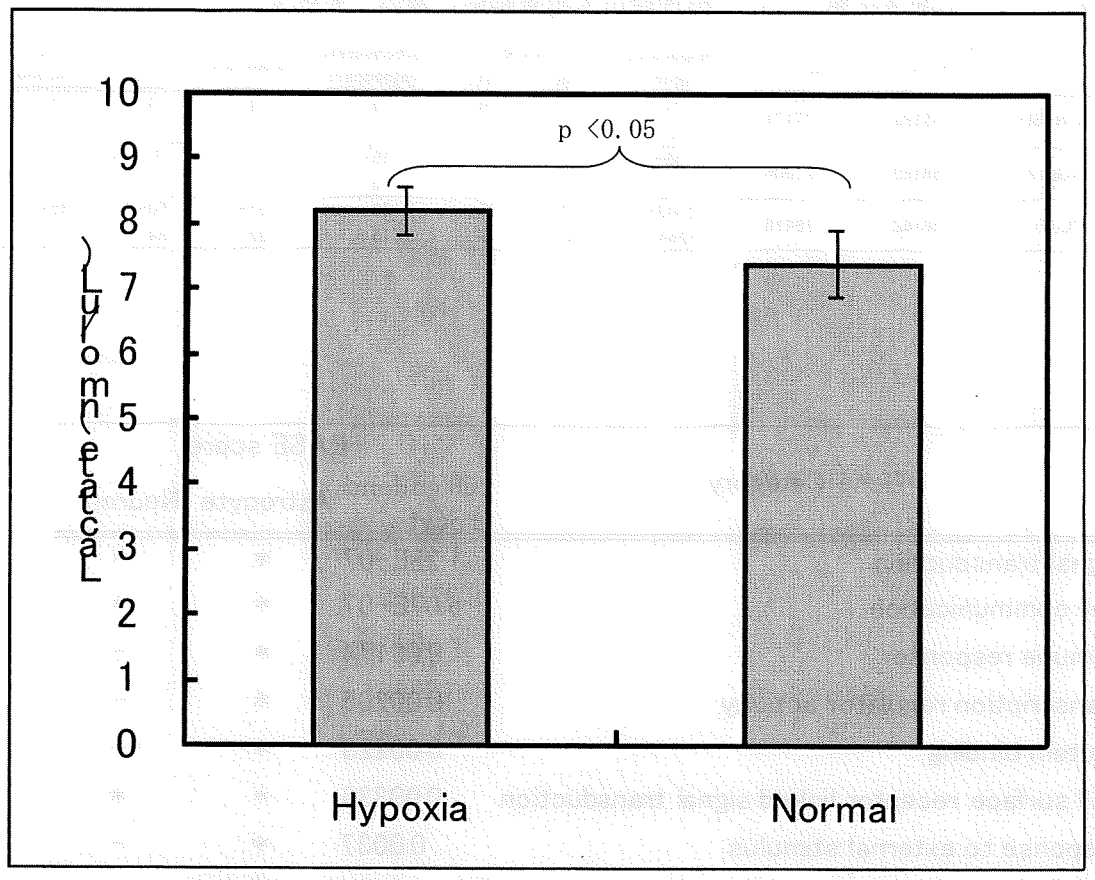
Height threshold $T = 4.00$, $p = 0.000$ (0.911) ($R=4$)
Extent threshold $k = 0$ voxels, $p = 1.000$ (0.911)
Expected voxels per cluster, $<k> = 6.557$
Expected number of clusters, $<c> = 2.43$
Expected false discovery rate, $<= 0.01$
Degrees of freedom = [1.0, 32.0]
FWHM = 6.9 10.6 9.7 mm mm mm; 4.4 5.3 4.9 {voxels}
Volume: 603560, 15420 voxels, 525.1 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 114.52 voxels)
Page 1

（資料１２：低酸素状態下での神経細胞由来・オリゴデンドロサイト由来培養細胞の細胞増殖とミトコンドリア活性）





（資料１３：低酸素状態下培養におけるＯＬ細胞培養液中の乳酸の濃度）



（資料１４：低酸素状態下での中枢神経由来培養細胞の遺伝子発現変化）

	Probe set	Expression	Responsive gene	Common SK	Common SV	Carbohydrate metabolism	Apoptosis	Cell cycle	Cell proliferation
SK-N-SH	58182	27171	7+	–	0	0	0	0	0
			64–	–	0	0	–1	0	0
SVGp12	58182	27006	155+	0	–	15+	3+	3+	6+
			15–	0	–	0	0	1–	2–
OL(H)	58182	25416	2100+	0	75+	46+	31+	60+	95+
			1264–	4–	5–	15–	22–	84–	97–

Gene Category	EASE score Oligodendrocyte	Astrocyte	Neuron
signal transduction	1.28E-07	*	*
cell communication	6.07E-07	*	*
immune response	0.00174	*	–
transcription regulator activity	0.00205	*	–
protein binding	0.00225	*	–
cell surface receptor linked signal transduction	0.00336	*	*
response to external stimulus	0.0037	*	–
glycolysis	0.00451	1.23E-05	–
protein modification	0.00574	*	–
cytoskeletal protein binding	0.00719	*	–
defense response	0.00736	*	–
soluble fraction	0.00737	*	–
cytoskeleton	0.00804	*	–
cellular process	0.00891	*	*
response to biotic stimulus	0.00908	*	–
carbohydrate metabolism	0.00916	1.34E-07	–

*:P<0.05