E．結論

認知症脳の縦断研究など同一個人の異なる時点におけるサンプル比較を目的に開発された tensor-based morphometry は、一卵性双生児ペアの全脳に対する voxel-based な定量的比較法として有用であり、かつ実用化可能であることが確認された。

F．健康危険情報

無し。

G．研究発表

無し。

H．知的財産権の出願・登録状況

無し。

図 1

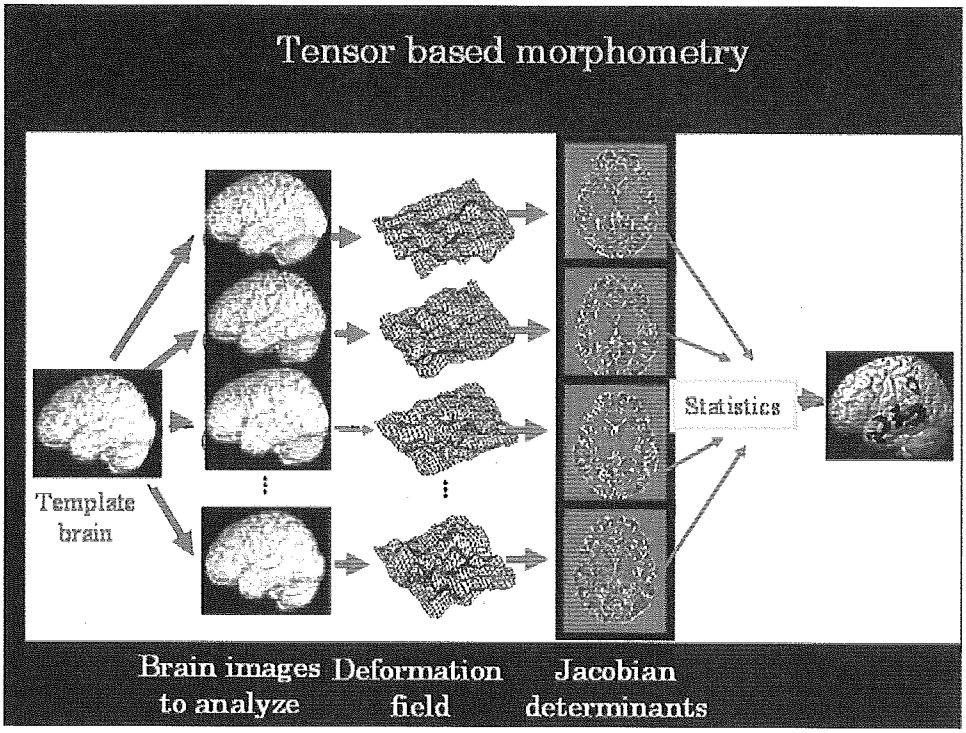

Tensor based morphometry
Template brain
Statistics
Brain images to analyze
Deformation field
Jacobian determinants

図 2

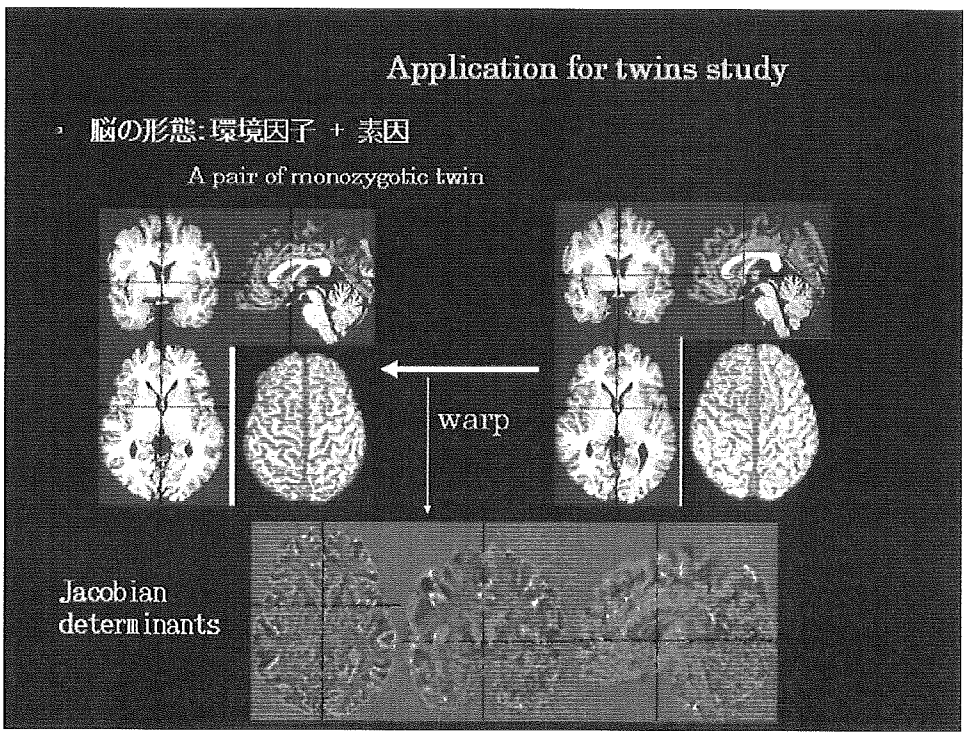

Application for twins study
脳の形態：環境因子 ＋ 素因
A pair of monozygotic twin
warp
Jacobian determinants

図 3

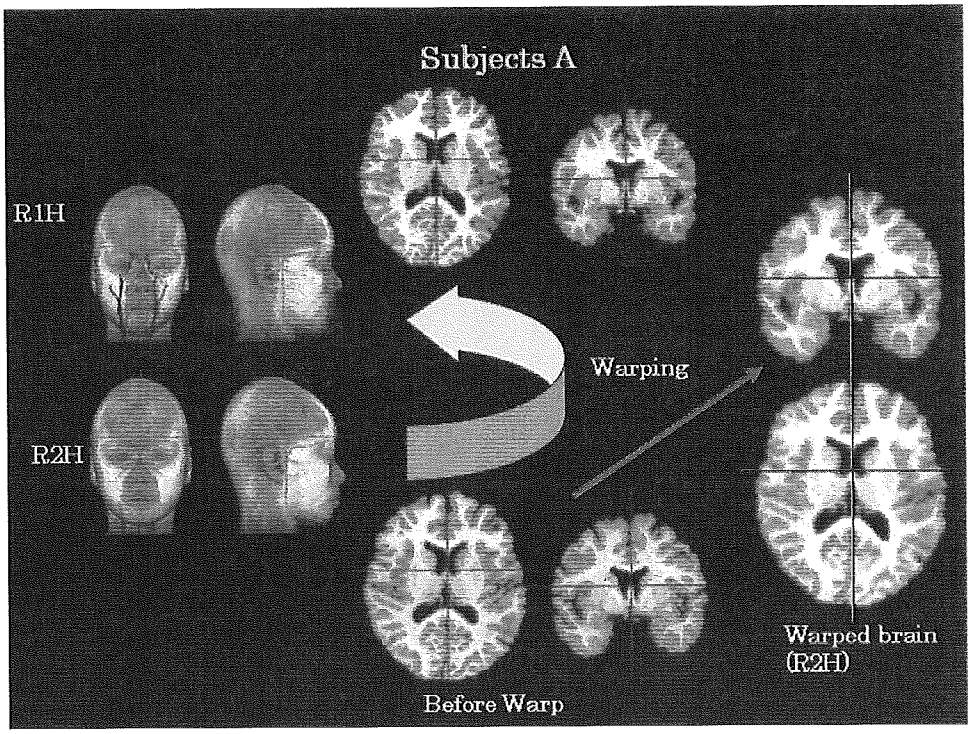

Subjects A
R1H
R2H
Warping
Warped brain
(R2H)
Before Warp

図 4

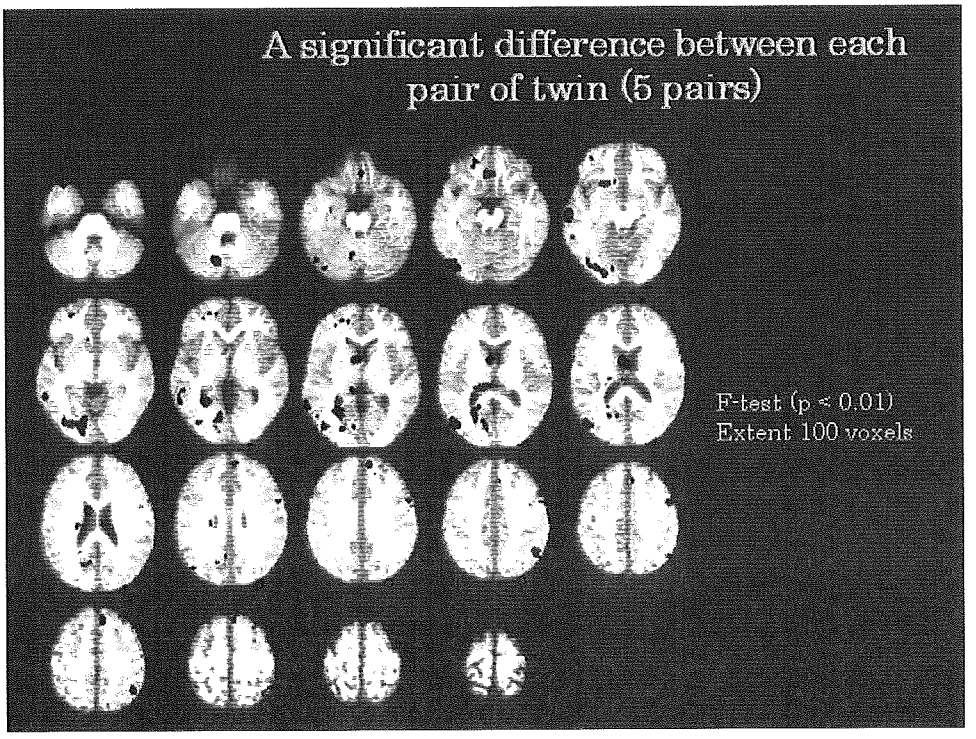
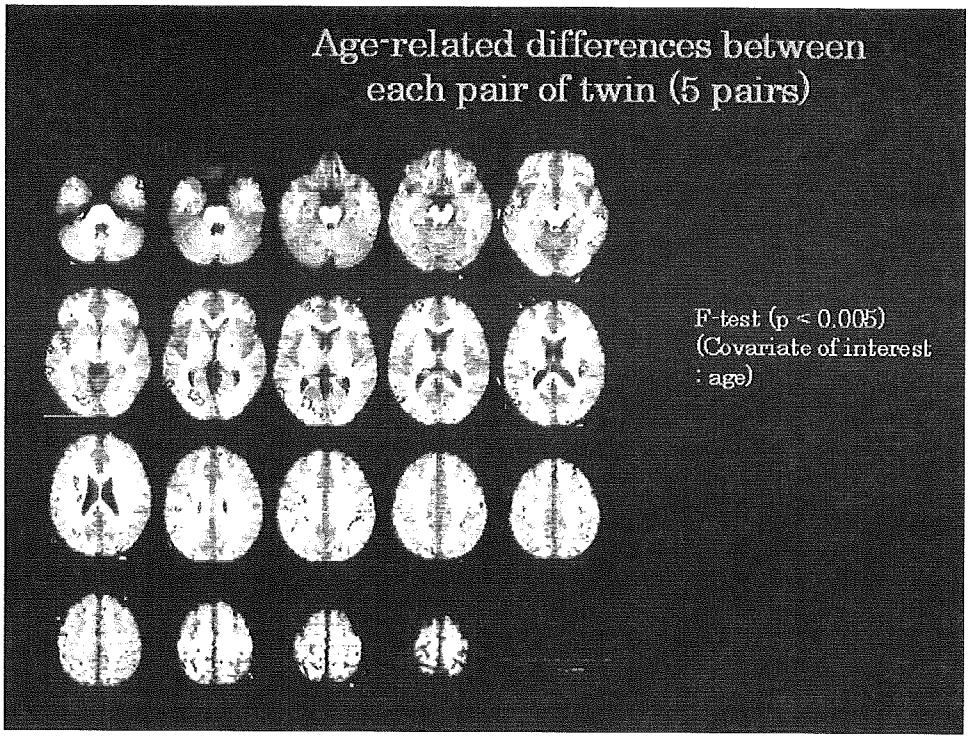

A significant difference between each pair of twin (5 pairs)
F-test (p < 0.01)
Extent 100 voxels

図5


Age-related differences between
each pair of twin (5 pairs)
F-test (p < 0.005)
(Covariate of interest
: age)

厚生労働科学研究費補助金（こころの健康科学研究事業）
平成17年度分担研究報告書

精神疾患における内因性レトロウイルスの関与についての検討

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研究要旨:
脳での潜在的転写活性を持つヒト内在性レトロウイルス(HERV)を網羅的に検索した。１１の期待されるHERVsを抽出した。そのうち、２つは実験によって検証することができた。更に、L1の網羅的検索をてがけている。
HERV-Kのメチル化レベルに個人差があること、個人間の順位は異なる臓器（胎盤及び胎児肝臓）で同じだった。これは、メチル化構築・維持能力としての総メチルC含量解析に末梢白血球が脳の代替物として利用できることを示唆する。

A 研究目的

脳での発現活性能を保持しているヒト内在性レトロウイルス(HERV)を網羅的に探索・同定する。更には、同様のL1を同定して、レトロトランスポゾンのメチル化状態と精神疾患との関連性を検討する。

B. 研究方法

RepbaseにHERVまたはHERV-likeと記録されている配列をQueryとしてBLASTによりヒトdbESTの電子スクリーニングを行う。検出したESTのグループ化により目的に適うローカスを絞り出し、ベンチワークでそれらの検証・確認を行った。

精神疾患患者での解析の予備実験として、典型的なHERVのメチル化解析とメチル化の組織特異性について、サザーンN法またはそれとbisulfite法の組み合わせで４種類の組織（16, 19, 21週の胎児脳・肝臓及び胎盤と成人末梢白血球）３例ずつのメチル化状態を併せて検討した。

（倫理面への配慮）

C. 研究結果

約600万個のヒトdbESTから963個のESTと764個のmRNAを検出した。これらのうち、11ローカスが脳での発現活性を期待できるものとして抽出された。胎児脳からのRNAを用いた実験で、1p36.13に局在するHERV（HUERS-P3b)と5p15.33に局在するHERVK9が脳での発現活性を保持するものと判断された。HERVのほか、発現活性能を持つL1の抽出作業を進めている。

HERV-Kのメチル化解析では、ほとんどのローカスがメチル化されていたが、比較的低メチル化状態にあるバンド（複数のローカス由来と考えられる）が有った。これは胎盤で顕著であり、肝臓でも脳及び末梢白血球に比べ低メチル化だった。胎盤で、このバンドのシグナル強度における個人差が明瞭に認められ、その順位は肝臓でも同じであった。

D. 考察

脳での発現活性能を保持しているHERVの検索を網羅的に行ったが、実験でその可能性を支持できるものが２つと少なかった。見落としもあるかもしれないが、確認作業の困難性も問題として残る。組織特異性からHERVを選んだが、別のレトロトランスポゾンであるL1を検索するともっと多数の活性型レトロポゾンを見出すことができるかもしれない。組織特異性が必ずしも必要でないことはRett症候群が示している。

HERV-Kメチル化の個人差の存在を見出したこと及びその順位が異なる臓器でも一致していたことは注目に値する。特に後者は、トータルレベルでのメチル化解析に限れば、精神疾患のメチル化解析に末梢白血球を用いることの妥当性を支持する根拠の１つとなるかもしれない。

E. 結論

データベースの充実のもとの網羅的検索にもかかわらず、期待した数をはるかに下回る潜在的転写活性保持型のHERV検出であった。検索での見落としもあるかもしれないが、検証法にも困難性が伴った。もっと時間を割いてでも、ベンチワークに入る前の実験デザインに工夫が必要である。精神疾患のメチル化解析には組織/マテリアルの問

題があるが、全ゲノムレベルでのメチル化解析には末梢白血球でも情報源となり得るかもしれない。

G. 研究発表

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H 知的財産権の出願・登録状況

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

Table 1 Southern blot analysis: primers for probe generation and wash conditions. *COMT* Catechol-O-methyltransferase, *DRD1* dopamine receptor D1, *DRD2* dopamine receptor D2, *NCAM* neural cell adhesion molecule, *HTR2A* 5-hydroxytryptaminereceptor 2A, *HCRT* hypocretin, *DRD3* dopamine receptor D3, *HTR3A* 5-hydroxytryptaminereceptor 3A, *HERV-K* human endogenous retrovirus K

Genes		Sense primer 5'-3'		Antisense primer 5'-3'	Washing Temp.
COMT		tctggtcggatctaggggagtct		gggctgggtgccttgtctaa	55°C
DRD1		agtggcattgttgttggctctga		ccctccggtgcctgtgct	56°C
DRD2		gaccaaggcgggacaccaat		ctgaaccgtccccctctcca	59°C
NCAM		cccgctttctccacccccctactttt		gccgttgctgggtgttgtttggata	52°C
HTR2A		agggaggaaagttgtctgctaat		ggggctggatttttgtcttc	57°C
HCRT		attgggcttggttttggcttctta		gcgctggcctgggacaat	59°C
DRD3		caaagccctgaggaaatggt		caaataaatgagtgccgagtaaga	52°C
HTR3A		tcgccttgctcctccccacac		gggaaaggacaaaaaggagag	55°C
HERV-K		gacttaatcctacggcaccaccta		agccctatttcttcggacctgttc	57°C

Table 2 A brief summary of PCR conditions and locations analyzed by the bisulfite method. *S* Sense-strand, *A* antisense-strand. Gene symbols as in Table 1

Gene	PCR	Primer 5'-3'	Length (location)[a]	Accession No.[b]	Annealing Temp.
COMT	1st	S: tttagttttttatttgggaaggg	290 bp	NM_000754	52°C
		A: acaaccctaactaccccaaaaac	(–239 to +51)	AC000090.3	
	2nd	S: tttttgagtaagattagattaagaggt	(43384-43673)		53°C
		A: acaaccctaactaccccaaaaac			
DRD1	1st	S: gttaggggttgattttaagagg	396 bp	NM_000794	54°C
		A: aaacactcccaaaactaatcaccta	(–305 to +91)	AC091393.3	
	2nd	S: tgagttttgtttttaggggatttaa	(111587-111982)		52°C
		A: accttcaaccctacaaaacaaaac			
DRD2	1st	S: gtygtagagttgtttagttttagtgt	239 bp	NM_000795	58°C
		A: crcacaaacttctaatcctaacct	(–45 to +194)	AP002840.3	
	2nd	S: gggtygggagttagggat	(111269-111507)		55°C
		A: crcacaaacttctaatcctaacct			
NCAM	1st	S: ggaaggttgggtagtaggag	335 bp	NM_181351	55°C
		A: cctaaaaacaaacaattaccaaac	(–284 to +51)	AP000802.5	
	2nd	S: gaaattttagttttttagggag	(95902-96236)		52°C
		A: atttttacaaaattatttcctacc			
HTR2A (upstream)	1st	S: tatyatattatgytggtggaagat	220 bp	NM_000621	46°C
		A: aaatacatccartrttaatcccata	(–741 to –521)	AL160397.17	
	2nd	S: tggtggaagatyaagaagagggga	(45919-46138)		57°C
		A: acaactttcctccctrraaattctcatt			
HTR2A (downstream)	1st	S: ttgattgtatgttatttaataatattgttgttaa	356 bp	NM_000621	52°C
		A: ttaatatacccacactctataacactaaaactaata	(–304 to +52)	AL160397.17	
	2nd	S: tgttattttaataatattgttgttaaattagtatt	(45346-45701)		51°C
		A: cacactctataacactaaaactaatatacatactat			
HCRT	1st	S: ttttttatgaaggaagaagg	410 bp	NM_001524	50°C
		A: ccaaaaaccttaaaactatc	(–399 to +11)	AC099811.7	
	2nd	S: gattgttgttggttgtttta	(57183-57592)		57°C
		A: tatcaattataacccactcc			
DRD3	1st	S: ggtaattaaattgaggaaggtgagag	283 bp	NM_000796	55°C
		A: ctaacaacaaacatacccaaacaaaac	(–210 to +73)	AC093010.7	
	2nd	S: aaaattaagattaaaaagagtattgaggag	(5952-6234)		53°C
		A: ctacttttccaacttccctattaaacc			
HTR3A	1st	S: tttttggggaaatatggttaagt	390 bp	NM_000869	52°C
		A: atcaaccaaatcctactacttcc	(–176 to +214)	AP000908.4	
	2nd	S: agttttttggttgaatgggtgga	(25226-25615)		55°C
		A: tctacttaccttctccctatacc			

[a]Locations relative to cDNA and genomic sequences/genes are indicated in the rows corresponding to the first and second rounds of PCR, respectively.

[b]GenBank accession numbers of cDNA and genomic sequences are described, with NM numbers indicating cDNA and other numbers the genomic sequences of genes.

Table 3 Primers and conditions for semi-quantitative RT-PCR. Gene symbols as in Table 1. Ex1a is the authentic first exon of HTR3A and Ex1b may be a novel exon (see Fig. 4 and text)

Gene	Sense primer 5'-3'	Antisense primer 5'-3'	Annealing Temp.	Cycles
COMT	agctcagaggagaccccagac	tgggctgcaggatgaactcgt	58℃	23, 26, 29
DRD1	tgcccccagcgaagtccacat	tcctgggcctctgctctgcta	62℃	28, 31, 34
DRD2	cgctgcagaccaccaccaact	gtcgatgctgatggcacacaa	58℃	25, 28, 31
NCAM	gcccaggtgcagtttgatgaa	ctgatctcacccagcccttg	58℃	20, 23, 26
HTR2A	tgctgctgggtttccttgtca	tctggagttgaagcggctgtg	58℃	27, 30, 33
HCRT	cggctaccccaccctgag	tcgtagaggcggcaagag	58℃	28, 31, 34
DRD3	tgcaggagccgaagtggtaaa	atgagcgcgcagtaggagagg	58℃	28, 31, 34
HTR3A	ggtgtgcgccccgtgagg	ccgtggggatggacaact	58℃	28, 31, 34
HTR3A (Ex1a)	cttgctcctccccacact	ccgtggggatggacaact	60℃	30, 33, 36
HTR3A (Ex1b)	tgctcttccaagccagat	ccgtggggatggacaact	58℃	30, 33,3 6
GAPDH	gaaggtgaaggtcggagtc	gaagatggtgatgggatttc	60℃	18, 21, 24

研究成果の刊行一覧表

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陣野　吉広

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資　　料

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Neuroscience Letters
www.elsevier.com/locate/neulet

Relationship between XBP1 genotype and personality traits assessed by TCI and NEO-FFI

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Received 6 June 2005; received in revised form 10 August 2005; accepted 12 August 2005

Abstract

There have been several researches on the role of personality in the pathophysiology of bipolar disorder. Recently, a polymorphism of XBP1, a pivotal gene in the endoplasmic reticulum (ER) stress response, was shown to contribute to the genetic risk factor for bipolar disorder. Therefore, in this study, we examined the relationship between the XBP1 gene polymorphism and the personality traits assessed by two self-rating scales, a shortened version of Temperament and Character Inventory (TCI) and NEO-Five Factor Inventory (NEO-FFI) in healthy subjects. The present results suggested that the XBP1 gene polymorphism was associated with the NEO-FFI score of neuroticism in female subjects. However, no significant differences in the other personality scale scores of both assessments were observed among normal subjects with −116C/C, C/G and G/G genotypes. Further investigations are necessary to examine the relationship in patients with bipolar disorder, or use full version of various self-rating personality assessments.

Keywords: XBP1; Polymorphism; Personality; TCI; NEO-FFI

Genetic factors significantly contribute to the determination of human personality traits although environmental influence is also important. Personality traits assessed by self-report questionnaires show moderate heritability [5]. Such inheritance is ultimately attributable to functional variants of genes programming brain development and function [4]. Some of these genes have also been implicated in the susceptibility to various psychiatric illnesses including mood disorders [5]. Several authors have paid attention to the premorbid personality traits of patients suffering from bipolar disorder. For example, Akiskal [1] showed that dysthymic, cyclothymic and hyperthymic temperaments represent putative development pathways to bipolarity in childhood and adolescence with clinically ascertained depressions. Bipolar patients might share a specific personality trait that represents the behavioral expression of some genetic neurochemical diathesis to the disease [2].

Recently, a polymorphism of XBP1 gene that plays a pivotal role in endoplasmic reticulum (ER) stress response was shown to contribute to the genetic risk factor for bipolar disorder [8], although negative findings were also reported [3,7]. Cell injury may develop under conditions where ER calcium homeostasis and, folding or processing of proteins is disturbed (referred to as ER stress), leading to the activation of unfolded protein response such as suppression of protein synthesis and expression of ER stress-related genes including *XBP1* [11]. The polymorphism (−116C → G) in the promoter region of the XBP1 gene was significantly more common in Japanese bipolar patients (odds ratio = 4.6). The XBP1-dependent transcription activity of −116G allele was lower than that of −116C allele, and induction of XBP1 expression after ER stress was markedly reduced in the cells with the G allele [8].

Therefore, it is possible that the XBP1 gene polymorphism may be involved in the development of personality specific for bipolar disorder. Recently, Kato et al. [9] reported a statistical trend for association between the XBP1 gene polymorphism and the Revised NEO Personality Inventory (NEO-PI-R) scores of

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doi:10.1016/j.neulet.2005.08.023

Table 1
TCI scores in healthy subjects sorted by -116C/G polymorphism of XBP1 gene

Sample	TCI subscales	XBP1 polymorphism			ANCOVA
		C/C	C/G	G/G	
Total	(N=248)	(N=24)	(N=116)	(N=108)	
	Novelty seeking	50.7 ± 4.9	50.1 ± 6.0	50.2 ± 7.0	F=0.10, p=0.91
	Harm avoidance	54.1 ± 8.5	52.7 ± 7.7	53.4 ± 9.0	F=0.36, p=0.70
	Reward dependence	43.5 ± 4.9	43.2 ± 5.2	42.9 ± 4.9	F=0.34, p=0.71
	Persistence	12.5 ± 2.1	13.2 ± 2.9	12.8 ± 2.7	F=1.47, p=0.23
	Self-directedness	68.4 ± 10.0	71.3 ± 9.6	69.3 ± 10.0	F=1.67, p=0.19
	Cooperativeness	72.8 ± 5.8	71.8 ± 6.7	71.3 ± 6.7	F=0.29, p=0.75
	Self-transcedence	26.8 ± 4.9	28.0 ± 6.4	26.9 ± 5.6	F=1.30, p=0.28
Male	(N=141)	(N=7)	(N=71)	(N=63)	
	Novelty seeking	48.9 ± 3.4	49.9 ± 6.0	50.1 ± 6.0	F=0.30, p=0.74
	Harm avoidance	51.6 ± 4.5	52.5 ± 8.0	51.8 ± 8.3	F=0.43, p=0.65
	Reward dependence	42.4 ± 4.9	42.6 ± 5.4	42.1 ± 4.8	F=0.43, p=0.65
	Persistence	13.4 ± 1.7	13.5 ± 2.8	12.6 ± 2.8	F=2.02, p=0.14
	Self-directedness	67.4 ± 6.9	69.8 ± 10.5	69.0 ± 10.1	F=0.10, p=0.91
	Cooperativeness	71.9 ± 7.0	71.1 ± 7.3	70.6 ± 6.5	F=0.14, p=0.87
	Self-transcedence	25.7 ± 4.3	27.9 ± 6.6	26.8 ± 5.7	F=0.54, p=0.58
Female	(N=107)	(N=17)	(N=45)	(N=45)	
	Novelty seeking	51.4 ± 5.3	50.3 ± 6.1	50.3 ± 8.2	F=0.16, p=0.85
	Harm avoidance	55.2 ± 9.6	52.2 ± 7.4	55.7 ± 9.5	F=1.97, p=0.15
	Reward dependence	43.9 ± 3.6	44.2 ± 4.6	44.0 ± 4.8	F=0.03, p=0.97
	Persistence	12.1 ± 2.2	12.8 ± 3.1	13.2 ± 2.5	F=1.25, p=0.29
	Self-directedness	68.8 ± 10.3	73.7 ± 7.2	69.6 ± 10.4	F=3.03, p=0.05
	Cooperativeness	73.2 ± 5.4	72.8 ± 5.5	72.3 ± 7.0	F=0.17, p=0.84
	Self-transcedence	27.2 ± 5.2	28.2 ± 6.3	27.0 ± 5.6	F=0.49, p=0.61

TCI scores are expressed as the mean ± S.D.

agreeableness and neuroticism in healthy Japanese female volunteers. In this study we examined the relationship between the −116C/G polymorphism of the XBP1 gene and the personality traits measured by two representative self-report questionnaires, Temperament and Character Inventory (TCI) and NEO Five Factor Inventory (NEO-FFI), in the Japanese healthy male and female subjects.

Two hundred and forty-eight biologically unrelated healthy volunteers were all Japanese recruited from laboratory, office or hospital staff at Hokkaido University. They all underwent a direct interview to exclude clinical and family history of psychiatric disorders classified according to DSM-IV. There were 141 males and 107 females, and the average age was 31.6 ± 9.1 (mean ± S.D.) years. After complete description of the study, informed consent was obtained from all subjects. The research protocol was approved by the ethics committee of Hokkaido University Graduate School of Medicine.

DNA was extracted from 20 ml of whole blood by standard methods. Genotypes for XBP1 gene −116C/G polymorphism were determined using the TaqMan 5′-exonuclease allelic discrimination assay, described previously [6]. Briefly, primers and probes for detection of the SNP are: forward primer 5′-CTGTCACTCCGGATGGAAATAAGTC-3′, reverse primer 5′-ATCCCTGGCCAAAGGTACTTG-3′, probe 1 5′-VIC-CTCCCGCACGTAAC-MGB-3′, and probe 2 5′-FAM-TCCCGCAGGTAAC-MGB-3′. PCR cycling conditions were: at 95 °C for 10 min, 45 cycles of 92 °C for 15 s and 60 °C for 1 min.

After collecting the blood samples, all subjects filled out a shortened version of TCI, which consists of 125 questions with four possible answers [10]. Each score on the 4-point scale can range from 1 (strongly disagree) to 4 (strongly agree). A part of the participants (206 subjects, 119 males and 87 females, age: 32.5 ± 9.4 years) completed NEO-FFI, the shortened version of the NEO-PI-R, which consists of 60 questions with 5-point scales. The validity and reliability of the Japanese version of TCI and NEO-FFI have already been confirmed among different Japanese populations [8,12].

Age and sex are known to affect self-rating personality assessments. In order to examine the relationships between the XBP1 gene polymorphism and, TCI or NEO-FFI scores, one-way analysis of covariance (ANCOVA) was performed with XBP1 genotype as independent variables, and with age and sex as covariates. Statistical test was carried out using SPSS for Windows. P values less than .05 were considered statistically significant after Bonferroni's correction for multiple testing.

The TCI and NEO-FFI scores sorted by the −116C/G polymorphism of XBP1 gene are shown in Tables 1 and 2, respectively. Observed genotype distribution was consistent with Hardy–Weinberg equilibrium. The distribution of the XBP1 genotype in our sample was almost same as in the other Japanese samples [8,9]. Although there was no significant relationship between the XBP1-116C/G genotypes and seven personality dimension scores of TCI (Table 1), the NEO-FFI score of neuroticism showed a significant association with the XBP1 gene polymorphism in females (F=6.41, p=0.003),

Table 2
NEO-FFI scores in healthy subjects sorted by -116C/G polymorphism of XBP1 gene

Sample	NEO-FFI subscales	XBP1 polymorphism			ANCOVA
		C/C	C/G	G/G	
Total	(N=206)	(N=20)	(N=98)	(N=88)	
	Neuroticism	29.4 ± 8.1	25.0 ± 6.7	26.2 ± 7.7	F=1.97, p=0.14
	Extraversion	23.2 ± 5.5	24.2 ± 9.1	22.0 ± 6.3	F=2.28, p=0.11
	Openness	29.6 ± 6.5	29.2 ± 5.4	29.1 ± 5.0	F=0.05, p=0.95
	Agreeableness	30.0 ± 5.4	28.4 ± 5.6	28.6 ± 5.0	F=0.51, p=0.60
	Conscientiousness	24.7 ± 8.5	26.3 ± 7.0	24.5 ± 5.8	F=1.50, p=0.23
Male	(N=119)	(N=7)	(N=61)	(N=51)	
	Neuroticism	23.7 ± 8.6	25.1 ± 6.9	24.9 ± 7.8	F=0.47, p=0.62
	Extraversion	24.3 ± 5.5	24.2 ± 10.6	21.8 ± 5.7	F=1.25, p=0.29
	Openness	28.9 ± 7.3	29.2 ± 5.7	28.6 ± 5.5	F=0.08, p=0.92
	Agreeableness	31.6 ± 4.7	28.2 ± 5.9	27.8 ± 5.2	F=1.45, p=0.24
	Conscientiousness	29.7 ± 8.4	26.7 ± 6.8	24.2 ± 5.7	F=2.87, p=0.06
Female	(N=87)	(N=13)	(N=37)	(N=37)	
	Neuroticism	32.5 ± 6.2	25.0 ± 6.3	28.1 ± 7.4	F=6.41, p=0.003
	Extraversion	22.6 ± 5.7	24.2 ± 6.1	22.3 ± 7.2	F=0.69, p=0.51
	Openness	30.0 ± 6.3	29.3 ± 4.9	29.7 ± 4.2	F=0.15, p=0.86
	Agreeableness	29.1 ± 5.7	28.9 ± 5.1	29.6 ± 4.7	F=0.15, p=0.87
	Conscientiousness	22.0 ± 7.5	25.6 ± 7.3	24.8 ± 6.0	F=1.32, p=0.27

NEO-FFI scores are expressed as the mean ± S.D.

not in male or all subjects (Table 2). No significant associations were observed in the other four dimension scores of NEO-FFI.

If some personality trait might be involved in the vulnerability of bipolar disorder, it should be a continuous factor from normal control to bipolar disorder. On the other hand, the G allele of XBP1 gene, a risk for bipolar disorder, is also observed in normal controls, not only in bipolar disorder [8]. Accordingly, it is of significance to examine the relationship between the XBP1 genotype and the personality traits in normal subjects. The present study partially confirmed the finding of Kato et al. [9] reporting a trend for association between the XBP1 gene polymorphism and the NEO-PI-R scores of agreeableness and neuroticism in healthy volunteers. In contrast to the previous report [9], the present study examined the relationship between the XBP1 genotype and the personality traits assessed by not only NEO but also TCI in both male and female healthy subjects. Thus, it clearly demonstrated that a significant association between the XBP1 polymorphism and the NEO score of neuroticism was observed only in female subjects. This finding suggests that gender differences exist in contribution of genetic factors to behavioral phenotypes. The discrepancy for the finding of agreeableness is unknown, but it may arises from the methodological difference between the two reports that the questionnaire used is full or shortened version of NEO. Further studies are necessary to examine the relationship between the XBP1 genotype and the personality traits in patients with bipolar disorder. The limitation of this study is to use the shortened version of TCI and NEO-PI-R. Analyzing subscales in each dimension might enable us to assess more specific facets related to the XBP1 gene polymorphism.

In conclusion, the present study suggests that the XBP1 gene polymorphism is associated with the NEO-FFI score of neuroticism in healthy female subjects. Further investigations are needed to examine the relationship in patients with bipolar disorder, or use full version of various self-rating personality assessments.

Acknowledgements

This work was partly supported by grants-in-aid for Soul and diseases-of-the-nervous-system research (T. Koyama) from Japanese Ministry of Health, Labor and Welfare, and for Scientific Research No. 15591206 (I. Kusumi) from Japanese Ministry of Education, Culture, Sports, Science and Technology.

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American Journal of Medical Genetics Part B (Neuropsychiatric Genetics) 136B:103–105 (2005)

Brief Research Communication

XBP1 Gene Polymorphism (-116C/G) and Personality

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Recently, a polymorphism of the *XBP1* gene (-116 C/G) was observed to play a significant role in the development of bipolar mood disorder from the Japanese population. The present study investigated a role of the polymorphism in the development of personality in healthy Japanese volunteers (n = 195). Personality traits were evaluated using NEO Personality Inventory-Revised (NEO PI-R). As a result, a statistical trend for association between the polymorphism (genotype) and the NEO PI-R scores of agreeableness and neuroticism was observed (ANOVA, $P = 0.01$ and 0.006, respectively). Subjects with the G allele, especially those with G-G genotype, tended to show lower neuroticism and higher agreeableness in the present study. The result is provisional and should be interpreted with caution, partly because the previous study suggested the allele as a risk allele for bipolar disorder. Further studies are required to confirm the results.

KEY WORDS: **XBP1 (-116C/G); personality traits; NEO PI-R; neuroticism; agreeableness; bipolar mood disorder**

INTRODUCTION

Genetic factors have a significant effect on the development of personality. Twin studies have suggested that approximately 30–60% of the variance of personality traits might be inherited [Tellegen et al., 1988; Bouchard, 1994; Ono et al., 2002]. A number of genes that affect the development and maintenance of brain functions and structure may be involved in the development of personality, interacting with other genes and environment. Genes that are associated with brain and/or mental disorders may therefore play a role also in the development of personality.

The *XBP1* gene plays a pivotal role in endoplasmic reticulum (ER) stress response [Yoshida et al., 2001]. Toxic metabolites or intermediate such as oxygen free radicals, in acute disorders and degenerative diseases including brain diseases, may cause ER stress and induce genes such as XBP1, which are involved in the stress response [Holtz and O'Malley, 2003; Paschen, 2003]. Recently, a polymorphism of the *XBP1* gene (-116 C/G) was observed to play a significant role in the development of bipolar disorder from the Japanese population [Kakiuchi et al., 2003]. The gene is located on 22q12, within a region which have been suggested for linkage both with bipolar disorder and schizophrenia [Badner and Gershon, 2002]. Expression of the *XBP1* gene in the brain has been confirmed [Kakiuchi et al., 2003]. While further studies are required for an elaborate description of the roles of the gene in the brain, those observations suggest that the *XBP1* gene and its polymorphisms may play a significant role in the development and/or functions of the brain, which could be related with the development of personality. The present study therefore explored a role of the -116 C/G polymorphism of the *XBP1* gene in the development of personality. Healthy volunteers from the Japanese population were studied using a personality questionnaire, NEO Personality Inventory-Revised (NEO PI-R).

MATERIALS AND METHODS

A total of 195 healthy Japanese volunteers (162 females and 33 males; age = 37.9 ± 12.0 years in females and 36.3 ± 11.0 years in males (mean ± SD)) were enrolled in the study. All subjects worked as medical staff (mostly nurses) in mental hospitals around Tokyo, Japan. They received a short interview by one of the authors and filled out questionnaires, to exclude clinical history of psychiatric disorders and current physical illnesses. Subjects with history of major psychosis including schizophrenia and mood disorders with episodes of major depressive disorder were also excluded, according to the information obtained at the interview and from the questionnaire. Written informed consent was obtained from all subjects. They donated their blood samples and filled out the Japanese version of the NEO PI-R. The NEO PI-R consists of 240 items and is designed to assess the five personality domains of neuroticism (vulnerability to stress), extraversion (sociability, assertiveness), openness (intellectual curiosity, unconventionality), agreeableness (altruism, sympathy), and conscientiousness (self-discipline, deliberation).

The *XBP1*-116C/G polymorphism was genotyped by PCR amplification with the primers of 5′-CGACAGAAGCAGAACTTTAG and 5′-CTGAGGTAATTCTCTGTTAG in a 12.5-μl volume containing LA Taq, dNTPs and 2 × GC buffer I (TaKaRa, Shiga, Japan). Genomic DNA was extracted from leukocyte using the standard method. Amplification conditions consisted of an initial 2 min at 94°C, 35 cycles of 30 sec at 94°C, 30 sec at 54°C, and 1 min at 72°C, followed by a final extension of 2 min at 72°C. Sequencing was performed using a commercial kit (BigDye terminator Cycle Sequencing Ready Reaction Kit, Applied Biosystems, Foster City, CA). Associations between the NEO PI-R scores and the *XBP1* -116C/G genotype were statistically analyzed using ANOVA, in females (n = 162) as well as all subjects (n = 195). Males were not separately studied due to its small sample size (n = 33).

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Received 15 December 2003; Accepted 8 June 2004
DOI 10.1002/ajmg.b.30098