研究成果の刊行に関する一覧表

書籍

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IV. 研究成果の刊行物・別刷

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GENETICS OF BIPOLAR DISORDER

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CONTENTS

Summary

Many linkage loci and candidate genes have been reported in molecular genetic studies of bipolar disorder. However, none of these findings have been consistently replicated. Meta-analyses of linkage studies have also reported conflicting results. Among recently reported candidate genes, BDNF, G72, AKT1, GRIN2A, XBP1, GRK3, HTR4, IMPA2 and GABRA1 may have some importance. Study of the possible roles of epigenetics or analysis of genetic diseases, in which bipolar disorder is one of phenotypes, may also be promising. In addition to monoaminergic and intracellular signaling pathways, recent studies have revealed possible roles for mitochondrial dysfunction, for glutamatergic dysfunction and for the endoplasmic reticulum stress pathway.

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Introduction

Bipolar disorder, also known as manic-depressive illness, is characterized by recurrent manic and depressive episodes, with a lifetime prevalence of approximately 0.8% (1). The patient's social life is

severely disturbed by behavioral problems during manic episodes, and individuals with this disorder also have a high mortality rate due to suicide. Three mood stabilizers, lithium, valproate and carbamazepine, are known to be effective for the prophylactic treatment of this disorder.

The role of genetic factors in the pathophysiology of bipolar disorder has been established based on twin, adoption and family studies. Twin studies revealed a higher concordance rate in monozygotic twins compared with dizygotic twins. This clearly indicates that genetic factors contribute to the onset of bipolar disorder (1). Moreover, the much higher concordance rate in monozygotic twins as compared to dizygotic twins suggests that multiple genetic factors are involved. Two adoption studies also showed a higher prevalence rate of mood disorders in biological parents compared with nurturing parents (2, 3). Family studies also supported a role for genetic factors in this disorder.

Linkage studies

The main strategies used to explore the genetics of bipolar disorder have gradually evolved from parametric linkage study, association study of candidate genes using case–control analysis, family-based association studies, nonparametric linkage analysis and haplotype analysis of candidate genes. However, the history of the molecular genetics of bipolar disorder is just like a roller coaster, characterized by two extremes, optimism and pessimism (4).

Although the paper published in *Nature* (5) reporting the linkage of bipolar disorder with chromosome 11 caused optimism, decreased evidence of linkage after disease onset in several family members caused pessimism that linkage studies of bipolar disorder are not reproducible (6). This event, caused by the phenocopy phenomenon, was the first setback in the molecular genetics of bipolar disorder.

However, after nonparametric linkage analysis became popular, relatively consistent results were obtained. This facilitated the use of linkage analysis again, and resulted in optimism.

To date, more than 22 genome-wide linkage analyses have been reported, but no locus has been replicated in any linkage studies. However, several loci were replicated in two or more linkage studies. The meta-analysis of linkage studies showed the evidence for linkage with 13q and 22q (7), while the other meta-analysis using raw data of the linkage studies reported the weak evidence of linkage with 9p21-p13.3, 10p11.22-q22.1, 1p32.1-p22.1, 19q13.2-qter, 9p13.3-q21.32, 17p13-q22, 18p11.23-q12.1, 18pter-p11.23 and 14q23.2-q32.11 (8). However, there was no evidence for linkage with chromosomes 13 and 22 in the latter study. The reason for this inconsistency is unknown.

Association studies

Genes participating in monoaminergic neurotransmission were good targets for earlier candidate gene studies (9). However, the results of these studies showed inconsistent results. Such inconsistency can be interpreted as reflecting type I error due to the small number of subjects or to genetic heterogeneity. Thus, family-based association analysis began to be used in larger populations in which genetic heterogeneity should be taken into account.

Among the polymorphisms of monoamine-related genes, some were found to cause functional alteration and to be associated with bipolar disorder in two or more studies. These include monoamine oxidase A (MAO-A) (10–12), serotonin transporter (HTT) (5HTT) (12–15) and serotonin 2C receptor (HTR2C) (14, 16). Catecol-*O*-methytransferase (COMT) is also included in such genes, although association was found only for rapid-cycling bipolar disorder (17, 18). However, the odds ratio was not large and the effects of publication bias cannot be totally ruled out.

Among recently reported candidate genes, association with brain-derived neurotrophic factor seems to be the most promising. Association with the Val66Met polymorphism of brain-derived neurotrophic factor was simultaneously discovered by a comprehensive association analysis of 90 single-nucleotide polymorphisms (SNPs) from 76 genes (19) and another candidate gene analysis (20). After that, this polymorphism was found to affect activity-dependent secretion of brain-derived neurotrophic factor and to alter hippocampal function and memory. However, association of brain-derived neurotrophic factor with bipolar disorder was not replicated in three additional studies in Japanese (21, 22) and Chinese (23).

Accompanied by the progress of rapid and high-throughput genotyping methods, haplotype analysis of many SNPs using mainly intron SNPs has become popular. This strategy was found to be productive in schizophrenia research; however, it has

the disadvantage of being unable to identify the functional polymorphisms responsible for the association.

G72 was initially found to be associated with schizophrenia, but later found to be associated with bipolar disorder (24). The association of G72 with bipolar disorder has been replicated in several subsequent studies (25–27). There is another gene encoding antisense RNA, G30, in this region. G72 protein was suggested to interact with D–amino acid oxidase and to be related to metabolism of D-serin, a modulator of the NMDA receptor. However, no functional polymorphism has been identified in this gene.

Other genes that showed association with bipolar disorder in at least two ethnicities, but for which no functional polymorphism was identified, include inositol monophosphatase (IMPA2) (28, 29), GABA receptor α1 subunit (30, 31) and serotonin 4 receptor (32).

As high-throughput genotyping methods continue to advance, whole-genome association analysis will become increasingly popular.

Mitochondrial DNA

When considered together, altered energy metabolism in the brain (33), a higher number of maternally transmitted pedigrees compared with paternally transmitted pedigrees (34) and comorbidity of mood disorders with mitochondrial disorders (35) suggest that mitochondrial DNA (mtDNA) might have pathophysiological significance in bipolar disorder. We therefore hypothesized that altered calcium signaling due to mitochondrial DNA mutations/polymorphisms may play an important role in bipolar disorder (35).

Kirk *et al.* (36) sequenced whole mitochondrial genomes in 25 bipolar disorder probands with maternally transmitted pedigrees. Although they found no specific mtDNA polymorphisms associated with bipolar disorder, they found fewer closely related haplogroups in bipolar disorder, suggesting that some unknown mtDNA polymorphism affects vulnerability to this disorder. McMahon *et al.* (37) sequenced whole mitochondrial genomes in nine probands with maternally transmitted pedigrees. Among the four polymorphisms nominally associated with bipolar disorder, mtDNA 10398G>A was the only one altering amino acid sequence. We also screened mtDNA polymorphisms in 43 bipolar patients and found that the mtDNA 10398G>A polymorphism was associated with bipolar disorder (38). This polymorphism was observed to alter intracellular calcium signaling (39).

Triplet repeat expansion

In bipolar disorder pedigrees, a phenomenon called "anticipation," *i.e.*, age at onset is lower in lower generations, has been observed (40). This phenomenon could be explained by trinucleotide repeat expansion. Using the repeat expansion detection method, expanded trinucleotide repeats of two genes, SEF2-1B at 18q21.1 and ERDA1 at 17q21.3, were identified in bipolar patients (41). Of these, SEF2-1B was reported to be expanded in bipolar disorder; however, subsequent studies did not support this association (42–44).

An approach from DNA microarray

Niculescu *et al.* (45) identified G-protein–coupled receptor kinase 3 as the gene upregulated after amphetamine administration using DNA microarray. They subsequently found that this gene was associated with bipolar disorder (46). However, no functional polymorphism has yet been identified.

Using pooled RNA samples from 10 bipolar patients and 10 controls, postmortem brain cDNA microarray analysis revealed a decrease in TGF-β1 in brains from bipolar patients (47). A study using serial analysis of gene expression (SAGE) reported an increase in NFκB (48). The downregulation of neuropeptide Y in the postmortem brains of schizophrenics identified by DNA micoroarray was also found in bipolar disorder (49).

We performed comprehensive DNA micoroarray analysis of the 50 postmortem brain samples, including 11 patients with bipolar disorder, obtained from Stanley Foundation Brain Bank (50). These results suggested that downregulated genes included receptors, channels and transporters, while upregulated genes included chaperones and stress proteins. Differentially expressed genes included a number of genes related to Ca^{2+} signaling, such as GRIK1, HTR2C, CACNA1A, GRM1 and LIM. Among the genes altered in the postmortem brains, differential expression was confirmed in lymphoblastoid cells for LIM and HSPF1. These findings suggest that this differential expression may reflect a genetic association (51). LIM encodes an adaptor protein linking N-type Ca^{2+} channel and protein kinase C (PKC). On the other hand, HSPF1 is a

molecular chaperone transporting proteins from mitochondria. This was increased both in postmortem brains and lymphoblastoid cells, which might reflect an upregulation secondary to mitochondrial dysfunction.

DNA microarray analysis of lymphoblastoid cells from lithium-responsive bipolar disorder patients identified that the α_{1B}-adrenergic receptor was upregulated in patients, but it decreased after lithium treatment (52).

We performed gene expression analysis using lymphoblastoid cells from two pairs of monozygotic twins discordant for bipolar disorder and found that two genes in the endoplasmic reticulum stress response pathway, XBP1 and HSPA5 (GRP78), were commonly downregulated (53). Case–control analysis revealed decreased endoplasmic reticulum stress response in lymphoblastoid cells from bipolar disorder patients. We found a polymorphism in the promoter region of XBP1, -116C>G, losing a binding site of XBP1 protein. This polymorphism altered the endoplasmic reticulum stress response and was associated with bipolar disorder in Japanese and NIMH pedigrees. Reduced endoplasmic reticulum stress response in bipolar disorder patients could be explained at least partly by this polymorphism. The impaired endoplasmic reticulum stress response due to this polymorphism was improved not by lithium but by valproate. These findings suggest that XBP1 polymorphism is a risk factor for bipolar disorder and could become a marker for treatment response. However, Cichon *et al.* (54) examined this polymorphism in a larger number of families and case–control samples and found that the -116 polymorphism of XBP1 was not associated with bipolar disorder. Another group also reported lack of association of this polymorphism with bipolar disorder (55). Thus, association of this polymorphism with bipolar disorder is not currently supported by clinical studies. We found that polymorphisms of HSPA5 (GRP78) were also significantly associated with bipolar disorder in Japanese but not in NIMH pedigrees (56). This finding suggests that there might be several functional polymorphisms in the endoplasmic reticulum stress response pathway which might confound the association analysis.

Response to maintenance lithium treatment was associated with the XBP1 polymorphism in one study (53). If this finding is replicated, this polymorphism could be used as a marker for treatment response. The locus of XBP1, 22q, is a common linkage locus to bipolar disorder and schizophrenia. Association of this polymorphism with schizophrenia was reported from two groups, including ours (57, 58).

Recently, Konradi *et al.* (59) performed gene expression analysis in the postmortem brains of bipolar disorder patients and found overall downregulation of mitochondria-related genes, which is compatible with our mitochondrial dysfunction hypothesis (35). However, gene expression of mitochondria-related genes could be affected by agonal factors (60) and needs further confirmation.

Overall downregulation of oligodendrocyte-related genes, initially reported in schizophrenia, has also been observed in bipolar disorder (61).

Nakatani *et al.* (62) performed comprehensive gene expression analysis of the hippocampus and cerebral cortex in an animal model of depression involving learned helplessness in rats. They found downregulation of serotonin 2A and IP3 receptors in the cerebral cortex, which may be relevant to the biology of bipolar disorder. Among the differentially expressed genes, they found downregulation of LIMK1, which has a LIM domain similar to LIM. The only gene altered in both of these two brain regions was NDUFV2, a gene encoding a subunit of mitochondrial complex I. NDUFV2 is located on 18p11, one of the replicated linkage loci. We found that the haplotype containing a functional polymorphism (-602A>G) that alters promoter activity was associated with bipolar disorder in Japanese and NIMH pedigrees (63, 64). Recently, NDUFV2 was found to be downregulated in the postmortem brains of patients with bipolar disorder (65). Taken together, these findings suggest that NDUFV2 plays an important role in the pathophysiology of bipolar disorder.

Relationship with schizophrenia

The possibility that bipolar disorder shares genetic vulnerability with schizophrenia has been suggested. Linkage analyses have suggested linkage of these two disorders with common loci such as 1q, 10q, 13q11, 18p11 and 22q11 (66). A report of the linkage of psychotic bipolar disorder with 13q and 22q also supports this finding (67). However, an extensive meta-analysis of linkage studies of bipolar disorder and schizophrenia has not shown commonly linked loci (68).

Association studies have also shown that several genes are associated with both of these two

disorders, *i.e.*, G72 (24), GRIN2A (69), AKT1 (70), IMPA2 (28, 29) and XBP1 (53). GRIN2A encodes the 2A subunit of the NMDA receptor. Association of bipolar disorder with GRIN1 (NMDA subunit 1) has also been reported (71). It is noteworthy that these glutamate-related genes are associated not only with schizophrenia but also with bipolar disorder. Recent findings suggest glutamatergic dysfunction in bipolar disorder. For example, mood stabilizers inhibit trafficking of AMPA receptors (72), and non-NMDA glutamate receptors GRIK1 and GRM1 were downregulated in the postmortem brains of bipolar disorder patients (50). This evidence suggests a possible role for alterations in glutamatergic neurotransmission in bipolar disorder.

A twin study reported on monozygotic twins, one of which had schizophrenia and the other bipolar disorder (73). Studies of neuroimaging, psychophysiology and neuropsychology have also showed common findings in these two disorders, *e.g.*, ventricular enlargement, increased dopamine D2 receptor binding potential, decreased D1 receptor binding potential, and decreased volume of the temporal pole and anterior cingulate (61). These results suggest that bipolar disorder and schizophrenia share a common molecular pathology.

Epigenetics

Since the results of genetic association studies are not consistent across studies, it has been postulated that epigenetic factors may also contribute to the disease (74). One of the reasons that we can postulate a role for epigenetics in bipolar disorder is the possible influence of parent-of-origin effect in this disorder. Parent-of-origin effect refers to the phenomenon in which the gender of the transmitting parent affects the onset and severity of the disease in offspring (75). The influence of parent-of-origin effect was reported in the linkage analysis of chromosome 18 in bipolar disorder (76). This phenomenon is observed when genomic imprinting is involved. Genomic imprinting is a phenomenon in which a maternally or paternally transmitted allele is inactivated by DNA methylation, and hemiallelic expression is therefore observed. Many imprinted genes are related to development, and some are related to behavior in animals (77). Thus, imprinted genes on chromosome 18 might be good targets for further study.

Pharmacological evidence also supports the hypothesis that DNA methylation is involved in the pathophysiology of bipolar disorder (78). Valproate is a histone deacetylase inhibitor and thus affects DNA methylation, while S-adenosyl methionine, which supplies methyl residue in DNA methylation reaction, is effective for bipolar depression.

Overall, there are relatively few studies on the epigenetics of bipolar disorder.

Bipolar disorder accompanied by genetic disease

Chronic progressive external ophthalmoplegia is an adult-onset, relatively mild mitochondrial myopathy caused by multiple deletions of mtDNA. It has been reported that autosomal dominantly inherited chronic progressive external ophthalmoplegia sometimes accompanies depression (79). Over the past several years, three autosomal genes responsible for chronic progressive external ophthalmoplegia have been identified. Among them, a mutation of adenine nucleotide translocator 1 (ANT1) was associated with a phenotype characterized by bipolar disorder and chronic progressive external ophthalmoplegia in all affected family members (80). Comorbidity of depression or bipolar disorder was reported in the families with mutations in the two other genes, polymerase gamma (81) and Twinkle (79, 82).

Wolfram disease is an autosomal recessive disorder characterized by many somatic symptoms such as hearing loss and diabetes. Accumulation of multiple deletions of mtDNA in the brain is reported in this disease (83). Patients with Wolfram disease frequently have bipolar disorder or depression (84). In addition, a higher frequency of depression and suicide was reported in nonaffected carrier of Wolfram disease mutations (85). These findings suggest that accumulation of multiple deletions of mtDNA may be one of the causes of bipolar disorder. Furthermore, we found that the 4977bp deletion of mtDNA was increased in lymphocytes (86) and in postmortem brains (87) in some cases. This finding further supports a role for mtDNA deletions in the etiology of bipolar disorder.

Another genetic disease linked with bipolar disorder is Darier's disease. Since the responsible gene, ATP2A2, encodes endoplasmic reticulum Ca^{2+}-ATPase, the relationship between bipolar disorder and ATP2A2 mutation has drawn attention (88).

Relationship with chromosomal abnormalities

Cases of bipolar disorder with chromosomal abnormalities suggest a possible relationship be-

tween bipolar disorder and several chromosomal regions: 11q21-25 (balanced translocation), 15q11-13 (deletion), 21q22 (trisomy), Xq27-28 (fragile X), 1q31-32 (fragile site) and 22q11-13 (deletion) (89).

DISC1 was cloned from the breakpoint of the balanced chromosomal translocation, (1;11)(q42.1; q14.3), which was linked with depression, schizophrenia and bipolar disorder (90). Recently, a role for DISC1 in neurite extension and localization to mitochondria has been reported (91). DISC1 may be related to the common pathophysiology of schizophrenia and bipolar disorder.

A family linkage of the balanced translocation t(9;11)(p24;q23) with mood disorders (five family members with bipolar disorder and one with recurrent major depression) was also reported (92). In this family, DIBD1, a gene cloned from the breakpoint 11q23, encoded mannosyltransferase, participating in *N*-glycosylation. DIBD1 expressed in the brain and a missense mutation, V289I, altering well-conserved amino acid, was identified. Although this was not associated with bipolar disorder, a weak linkage with an intron polymorphism was seen. This interesting gene needs further study.

Conclusion

As described above, the molecular genetic study of bipolar disorder has accelerated in recent years. DNA microarray and high-throughput genotyping methods have facilitated such study. In addition, the number of researchers investigating mental disorders has increased considerably, further promoting the possibility of advancement in this field. Hopefully, the current optimism concerning the future of the molecular genetic study of bipolar disorder will not end as a daydream.

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LETTER TO THE EDITOR

Lithium response and −116C/G polymorphism of *XBP1* in Japanese patients with bipolar disorder

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Three mood stabilizers, lithium, valproate and carbamazepine, are known to be effective for a subset of patients with bipolar disorder, but the mechanism(s) of action for these three drugs is controversial (Gray et al., 2003). The response to treatment varies among individuals, but to date, no biological marker for predicting treatment response has been identified (Ikeda and Kato, 2003). Several groups have been pursuing a genetic marker that can be used to predict treatment response to lithium. Several polymorphisms of the genes such as serotonin transporter (Del Zompo et al., 1999; Serretti et al. 2001), tryptophan hydroxylase (Serretti et al., 1999) and inositol polyphosphate 1-phosphatase (Steen et al., 1998), have been suggested to relate to the lithium response, but these findings are still controversial. Thus, clinicians select mood stabilizers only empirically.

We recently identified a functional single-nucleotide polymorphism, −116C/G in the promoter region of the *XBP1* gene, which alters the endoplasmic reticulum stress response. The functional impairment caused by this substitution can be rescued by treatment with valproate (Kakiuchi et al., 2003). Since lithium and carbamazepine did not improve the impairment caused by the −116G polymorphism in vitro, we hypothesized that lithium, the first-choice drug for bipolar disorder, is not effective for patients with a −116G/G genotype. To test this hypothesis, we investigated the possible association between the treatment response to lithium and *XBP1* genotype.

The subjects were 56 patients with bipolar disorder [aged 46.8 ± 13.4 yr (mean ± S.D.), 38 females and 18 males, 38 with bipolar I disorder and 18 with bipolar II disorder]. Their serum lithium concentrations were maintained at therapeutic concentrations (0.4–1.3 mM). When their serum concentration was less than 0.3 mM, it was considered as non-compliance. All subjects were Japanese and gave written informed consent to participate. The ethics committees of participating institutes approved this study. Consensus diagnosis by at least two senior psychiatrists according to the DSM-IV criteria (American Psychiatric Association) was made for each patient using an unstructured interview and by scrutinizing medical records. Response to maintenance lithium treatment was retrospectively assessed by reviewing the chart records. During maintenance treatment, use of certain additional drugs was allowed, but the addition of antidepressants or antipsychotics was regarded as a relapse.

The subjects were classified into three groups with regard to lithium response; these groups were as previously defined (Kato et al., 2000). In brief, lithium responders (responders) had no relapse during maintenance lithium treatment. Lithium partial responders (partial responders) showed decreased frequency or severity of relapse during maintenance lithium treatment compared to before the initiation of lithium treatment. Lithium non-responders (non-responders) had relapses during lithium treatment. Patients were excluded when their compliance was poor. Patients diagnosed as 'rapid cyclers' were regarded as non-responders. These clinical assessments were performed blind to *XBP1* genotype, which was determined by PCR direct sequencing (Chen et al., 2004; Kakiuchi et al., 2004).

Among 56 cases, 10 patients were judged as responders, 24 patients as partial responders, and 22 patients as non-responders. There was no significant difference in the duration of observation period among the three groups [responders, 30.1 ± 35.3 (mean ± S.D.) months; partial responders, 74.5 ± 86.0 months; and non-responders, 43.1 ± 47.0 months; $p = 0.13$, d.f. = 2, one-way ANOVA], nor between the responders and the combined group of partial and non-responders ($p = 0.21$, χ^2 test). Patients with the −116G/G genotype showed a significantly smaller proportion of responders, compared to −116C/C or −116C/G patients ($p = 0.049$, χ^2 test; Table 1).

Our results suggest that lithium may not be effective for bipolar patients with the −116G/G genotype in the promoter region of *XBP1*. This finding seems to be in accordance with our in-vitro data showing that only

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Table 1. Relationship between *XBP1* (−116) genotype and lithium response in bipolar disorder

	Genotype responders	Partial responders (PR)	Non-responders (NR)
C/C	1	1	0
C/G	7	9	11
G/G	2	14	11
		PR and NR	
C/C or C/G	8	21	
G/G	2	25*	

* $p < 0.05$ by χ^2 test.

valproate could improve the functional impairment caused by the G/G genotype (Kakiuchi et al., 2003). However, the association between *XBP1* genotype and lithium response was not significant after Bonferroni correction of all possible comparisons. In addition, we did not observe a significant difference between genotypes when the combined group of partial responders and responders was compared with non-responders. Thus, it cannot be ruled out that this difference was a statistical false-positive, which resulted from the small sample size. A study using a larger number of subjects should be performed.

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Statement of Interest

The authors declare competing financial interests. RIKEN has a pending patent on the results of this paper.

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Lack of support for a genetic association of the *XBP1* promoter polymorphism with bipolar disorder in probands of European origin

To the editor:

Kakiuchi and colleagues[1] reported that variation in the gene *XBP1* contributes to susceptibility to bipolar affective disorder (BPAD). They identified a functional promoter polymorphism of *XBP1* (−116C→G) and reported association of the G allele with BPAD in 197 Japanese probands and 451 Japanese controls and in 88 trios from the National Institutes of Health (NIMH) Genetics Initiative collection of (mainly) European American families identified through a sibling pair with BPAD. They also reported evidence that constructs carrying the G allele resulted in an *in vitro* cellular phenotype that was reversed by valproate, an effective treatment for BPAD.

We examined the −116C→G polymorphism in four family-based BPAD samples comprising 586 families: (i) 147 families from the NIMH Genetics Initiative Waves 1 and 2, including the 88 trios studied by Kakiuchi *et al.*[1]; (ii) 176 families from the NIMH Wave 3, identified in a similar manner as the earlier waves; (iii) 173 Bulgarian trios, identified through a proband having DSMIV (ref. 2) bipolar I disorder (BPI); and (iv) 90 similarly identified UK parent-proband trios with DSMIV (ref. 2) BPI.

Our results do not support a significant association of −116C→G with BPAD in any of these four samples (Table 1). We reproduced the finding of Kakiuchi *et al.* in the trios that they studied but not in the complete NIMH Waves 1 and 2 sample from which those 88 trios were drawn. The subset of trios studied by Kakiuchi *et al.* has a significantly earlier age at onset of illness than the other Wave 1 and 2 samples. To account for this, we tested for an interaction between genotype and age at onset but found none. Consistent with the NIMH trio results, there was also no evidence for an interaction between genotype and age at onset in the Bulgarian or UK trios.

We also found no evidence for association of the G allele with BPAD in three case-control samples, comprising 1,181 individuals with DSMIV BPI and 1,717 nonpsychiatric ethnically matched controls (UK, 580 affected individuals and 617 controls; Germany, 300 affected individuals and 789 controls; Poland, 301 affected individuals and 311 controls). Data were consistent with Hardy-Weinberg equilibrium and distributions of genotypes and alleles were similar between cases and controls (**Supplementary Table 1** online).

Kakiuchi *et al.* examined eight markers to test for population stratification as a potential cause of their case-control findings. Similarly, we examined six SNPs and one STR marker, taken from unlinked chromosomal regions, with STRUCTURE[3]. We found no evidence for population stratification that might mask an association of *XBP1* in our data. Recent studies suggest that a larger number of markers is usually necessary to rule out population stratification[4,5].

The results in our trio samples from different European and European American populations are mutually consistent and not supportive of the finding of association by Kakiuchi *et al.*[1]. Inadequate power is an unlikely explanation of our results. Our combined family sample is approximately seven times larger than that used by Kakiuchi *et al.*, providing at least 80% power to detect at $P < 0.05$ a heterozygote relative risk of 1.32 (ref. 6; smaller than that estimated by Kakiuchi *et al.*[1]), if present in any one sample. Our findings are supported by our case-control sample, which is approximately six times larger than that used by Kakiuchi *et al.* Each sample had power >0.99 to replicate the effects reported by Kakiuchi *et al.* (calculated by the Genetic Power Calculator[6]).

How are we to reconcile our findings with those of the previous study? One possibility is that Kakiuchi *et al.* unwittingly chose probands with more severe illness, characterized by earlier onset, and that only in this subset is *XBP1* etiologically relevant. This is unlikely, because we found no interaction between genotype and age at onset and Kakiuchi *et al.* apparently used unselected cases for both their family-based and case-control studies. It is also possible

Table 1 Family-based association analysis of *XBP1* −116C→G

Sample	Number of trios or pedigrees	Transmission ratio (TDT)	Test-statistic[a,b]	*P* value[b]
Subset of NIMH Waves 1 and 2, used by Kakiuchi *et al.*[1]	88 trios	1.56	3.98	0.046
NIMH Waves 1 and 2 complete	147 pedigrees	–	1.61	0.2
NIMH Wave 3	176 pedigrees	–	0.07	0.79
Bulgarian trios	173 trios	0.97	0.03	0.86
UK trios	90 trios	0.86	0.45	0.5

[a]χ^2 with 1 degree of freedom. NIMH Waves 1, 2 and 3 were analyzed by PDT[7], as not all trios were complete and multiple siblings per family were used to extract the maximal information. All other samples consist of complete trios and were analyzed by TDT[8]. [b]For PDT tests, test statistics and *P* values using the 'average' option are shown. Results did not differ significantly with the 'sum' option.

that, although the finding of association by Kakiuchi *et al.* was in a sample of European ancestry, the −116 C→G polymorphism contributes to BPAD mainly in populations of Asian origin. Alternatively, it is possible that the polymorphism is in linkage disequilibrium with the true functional polymorphism and differential linkage disequilibrium patterns obscure the association. Although this is possible, the functional data that comprise much of the evidence presented by Kakiuchi *et al.* depend on −116C→G itself being the susceptibility variant.

The biological data in the original report remain interesting, but we believe our data indicate that the reported genetic association represents a type I error resulting from random variation in small samples. It is possible that there is a small, population-specific effect of *XBP1* on the development of BPAD. This would best be tested in a large, independent sample of Japanese origin.

Note: Supplementary information is available on the Nature Genetics website.

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In reply:

We previously concluded that an impaired XBP1 loop is a genetic risk factor for bipolar disorder[1] based on multiple lines of evidence: (i) downregulation of *XBP1* and *HSPA5* in twins discordant for bipolar disorder; (ii) reduced response of *XBP1* and *HSPA5* to endoplasmic reticulum (ER) stress in cells lines established from individuals with bipolar disorder; (iii) identification of a functional polymorphism, −116C→G, in the promoter of *XBP1*; (iv) association of this polymorphism with bipolar disorder in Japanese case-control samples; (v) confirmation of this association in a small number of European American trios; and (vi) improvement of the functional impairment due to the −116G allele by valproate. The findings of Cichon and colleagues, by genotyping enough samples of European origin to test our finding, indicate that the fifth finding was type I error. We agree that the association in Japanese individuals should be tested in larger number of independent samples.

So far, no genetic associations with bipolar disorder have been consistently replicated. The endophenotypes may be common among ethnicities, but the genetic risk factors responsible for the endophenotypes may be different between populations, as suggested by the difference in allele frequencies of −116C→G between European Americans and Japanese[1]. Thus, other genes in the ER stress response pathway also need to be examined.

We recently investigated the next candidate gene, *HSPA5*. Its expression was downregulated in affected twins, and its response to ER stress was reduced, like *XBP1* (ref. 1).

By screening all exons and the upstream region (1 kb) of *HSPA5* in 24 Japanese individuals with bipolar disorder, we found that the entire *HSPA5* gene was in one haplotype block consisting of four main haplotypes. By genotyping three key polymorphisms (−370C→T (nucleotide position from the