

Possible association between haplotypes of the *FKBP5* gene and suicidal bipolar disorder, but not with melancholic depression and psychotic features, in the course of bipolar disorder

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Abstract: We aimed to analyze the association between polymorphisms of the *FKBP5* (*FK506 binding protein 5*) gene and subtypes of bipolar disorder. In the study, we included 195 bipolar disorder patients with psychotic features, 129 bipolar patients with melancholic depression, and 156 bipolar patients with a history of suicidal attempts. We found weak association between the haplotypes of the *FKBP5* gene and bipolar patients with suicidal attempts. We did not find an association between polymorphisms of the *FKBP5* gene and bipolar disorder with psychotic features, nor with bipolar disorder with melancholic depression. Limitations of our study are the absence of data about previous trauma exposure and the small sample size of patients, which of course can lead to false-positive results, so further validation and replication of the present findings are still needed.

Keywords: *FKBP5* gene, bipolar disorder, melancholic depression, psychotic features, suicide attempts

Introduction

Bipolar disorder is thought to originate from the interactions between susceptibility genes and adverse environmental stresses. The hypothalamus–pituitary–adrenal (HPA) axis is a major system involved in stress response, and its dysregulation is an important element in the pathogenesis of affective disorders.¹ A dysregulation of the stress hormone is one of the most potent biological findings in stress-related disorders, including depression, especially melancholic depression. Stress is also seen as one of the factors predisposing both to occurrence of psychotic features and suicidal attempts.

HPA-axis reactivity is regulated by negative-feedback mechanisms induced by mineralocorticoid and glucocorticoid receptors. The activity of the glucocorticoid receptor (GR) is regulated by the *FKBP5* (*FK506 binding protein 5*) gene.² The binding of *FKBP5* to the GR complex decreases the affinity of cortisol binding, followed by a deficient receptor nuclear translocation, and therefore reduces GR sensitivity.³ GR activation elicits expression of *FKBP5* messenger ribonucleic acid and protein and this yield to ultrashort feedback loop, affecting GR sensitivity.⁴ Alterations in the HPA axis in response to stress may be associated with functional polymorphisms in genes encoding those receptors.^{5,6} Menke et al⁴ suggested that depressed patients carrying the *FKBP5* rs1360780 allele T exhibit significant GR resistance compared with healthy controls. The results obtained by Menke et al⁴ were measured by a

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dexamethasone-suppression test, which caused (only in depressed patients) suppression of adrenocorticotrophic hormone and plasma cortisol concentrations.⁴

Zimmermann et al showed that there is association between the genotypes of the *FKBP5* gene, trauma, and onset of depression.⁷ Other single-nucleotide polymorphisms (SNPs) of the *FKBP5* gene – rs4713916, rs1360780, and rs3800373 – are associated with the deficient normalization of stress-induced cortisol secretion in healthy humans after psychosocial stress.^{8,9}

In regard to suicide, *FKBP5* gene expression was reduced in the amygdala of suicide victims,³ and analysis of haplotypes of the *FKBP5* gene in suicidal patients showed an association in previous studies.^{10,11}

We hypothesized that genetic variation in the *FKBP5* gene might be one of the factors influencing dysfunction of the HPA axis and altering the risk as well as the course of bipolar disorder and its subtypes. As there have been few studies performed so far on depressive disorder and suicidal patients, and none to our knowledge on bipolar patients having psychotic features nor with melancholic depression in the course of bipolar disorder, we aimed to analyze the eight polymorphisms in relation to the subtypes of bipolar disorder.

Methods

Patients

The study was performed on a group of 528 bipolar patients, among which 195 had a history of psychotic features, 129 had a history of melancholic depression, and 156 had a history of suicide attempts. Patients were recruited from inpatients of the Department of Adult Psychiatry, Poznań University of Medical Sciences, living in the Wielkopolska region of Poland. This region is considered ethnically homogeneous.¹² The mean age of onset was 31.6 years, standard deviation (SD) 11.5, overall mean number of episodes was eleven, and among those depressive episodes six and manic episodes five. The mean age of patients was 44.36 years, SD 13.9. Consensus lifetime diagnosis by at least two experienced psychiatrists was made for each patient. The phenotyping of patients was based on medical records, family history, and clinical interviews according to *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) criteria using the Structured Clinical Interview for DSM Disorders.¹³

Control group

The control group consisted of 742 subjects. Control subjects were recruited from the group of healthy volunteers, blood donors, and hospital staff and students of the University of Medical Sciences in Poznań and the Clinical

Neuropsychology Unit, Collegium Medicum Bydgoszcz. Only 40% of the control group were psychiatrically screened, which is the main limitation of this paper. The mean age was 37.7 years, SD 12.5. After complete description of the study, written informed consent was obtained. The study was performed in compliance with the Declaration of Helsinki and was approved by the local bioethics committee.

Genotyping

Deoxyribonucleic acid (DNA) was extracted using the salting-out method.¹⁴ The list of SNPs analyzed and the ID numbers of TaqMan assays are shown in Table 1. SNP selection included the following criteria: high frequency (minor allele frequency [MAF] >0.05; the MAF for our group [shown in Table 2] was the same as in the Caucasian population [CEU population from HapMap] shown in Pub Med), indication as tag SNP in HapMap, or previously reported associations for psychiatric disorders (both positive and negative findings). SNPs chosen covered noncoding regions (introns, untranslated regions) possible to affect gene regulation. The eight polymorphisms were genotyped with TaqMan Genotyping Master Mix and TaqMan SNP genotyping assays (Life Technologies, Carlsbad, CA, USA).

All the assays were validated and predesigned. Reaction components and amplification parameters were based on manufacturer's instructions. The ABI Prism® 7900HT (Life Technologies) sequence-detection system was used for amplification for TaqMan SNP genotyping assay plates. SDS version 2.1 (Life Technologies) software was used for data acquisition and analysis. The same software was used for the allelic discrimination-analysis module.

Plate genomic control DNA samples and nontemplate controls (water) were included for each reaction. The TaqMan SNP genotyping assay was controlled (25% of randomly chosen samples from both groups) to check for genotyping accuracy. Identical genotypes were identified in all repeated samples. The diagnosis of the subjects during genotyping was not known.

Table 1 *FKBP5* gene polymorphism description

SNP	Substitution	Location	Method	Assay ID
rs1360780	C/T	Intron 9	TaqMan	C__8852038_10
rs755658	C/T	Intron 3	TaqMan	C__594063_20
rs9470080	C/T	Intron 10	TaqMan	C__92160_10
rs4713916	A/G	Intron 10	TaqMan	C__1979246_10
rs7748266	C/T	Intron 8	TaqMan	C__29802748_10
rs9296158	A/G	Intron 6	TaqMan	C__1256775_10
rs9394309	A/G	Intron 10	TaqMan	C__1256794_20
rs3800373	A/C	3' UTR	TaqMan	C__27489960_10

Abbreviations: SNP, single-nucleotide polymorphism; *FKBP5*, *FK506 binding protein 5*; UTR, untranslated region.

Statistical analysis

To test for differences in genotypic and allelic distribution, the two-tailed Pearson χ^2 test and Fisher's exact test were used. Chi-square was used for 3×2 contingency tables to compare genotypes (three different) between cases and controls. Fisher's exact test was used for 2×2 contingency tables to compare allele frequencies between cases and controls. Two-tailed power analysis was also performed, using Statistica version 8.0 (StatSoft, Tulsa, OK, USA). A demo of the InStat 3 (GraphPad Software, La Jolla, CA, USA) program was used to calculate odds ratios. Linkage disequilibrium between polymorphisms of the *FKBP5* gene was examined by pair-wise comparisons of r^2 and D' using Haploview version 4.1 (Broad Institute, Cambridge, MA, USA).¹⁵ The same software was used to haplotype construction using an expectation–maximization algorithm. Correction for multiple testing was performed for multiple comparisons: in haplotype analysis using 10,000 permutations implemented in the Haploview software. Quanto version 1.2.3 with odds-ratio values between 1.1 and 1.4 for two-sided associations was used for power calculations.

Results

Hardy–Weinberg equilibrium analysis

All the analyzed SNPs were in Hardy–Weinberg equilibrium concordance for the controls. The only SNP of the *FKBP5* gene that was not in concordance with the Hardy–Weinberg law (results shown in Table 2) was rs7748266 in the group of patients with psychotic features ($P=0.03$), as SNPs in Hardy–Weinberg disequilibrium are less powerful and do not tend to increase false-positive results.¹⁶ We did not exclude this SNP from the study.

Genotyping and allele frequencies

In Table 2, check markers (showing if this marker, eg, SNP, is valid for such analysis as success rate) for subtypes of BP for the *FKBP5* gene are shown. The success rates for genotyping were between 96.03%–98.97%, and for all the polymorphisms, genotyping error rates were $<1\%$.

Genetic association analysis

We found association with haplotypes CCATTGT ($P=0.0123$) and CCACTAT ($P=0.0235$) in bipolar patients with suicidal attempts, but not in bipolar patients with

Table 2 Check markers for subtypes of BP for *FKBP5* gene

Number	SNP	Pos chromos	ObsHET	PredHET	HWE	% zgenotyp	MAF	Alleles
Check markers melancholic								
1	rs3800373	35650454	0.366	0.366	1.0	99.2	0.241	A:C
2	rs755658	35657648	0.168	0.168	1.0	95.4	0.092	C:T
3	rs9296158	35675060	0.365	0.373	0.5832	98.3	0.248	G:A
4	rs7748266	35700722	0.213	0.226	0.1241	97.3	0.13	C:T
5	rs1360780	35715549	0.365	0.374	0.4929	97.4	0.249	C:T
6	rs9394309	35729759	0.376	0.387	0.4897	96.4	0.262	A:G
7	rs9470080	35754413	0.399	0.4	0.9398	98.9	0.277	C:T
8	rs4713916	35777961	0.37	0.379	0.5371	98.2	0.254	G:A
Check markers psychotic								
1	rs3800373	35650454	0.367	0.37	0.879	98.9	0.245	A:C
2	rs755658	35657648	0.168	0.167	1.0	95.4	0.092	C:T
3	rs9296158	35675060	0.364	0.377	0.3189	98.3	0.252	G:A
4	rs7748266	35700722	0.222	0.24	0.0375	97.1	0.139	C:T
5	rs1360780	35715549	0.369	0.38	0.4012	97.2	0.255	C:T
6	rs9394309	35729759	0.391	0.396	0.7577	96.2	0.272	A:G
7	rs9470080	35754413	0.408	0.408	1.0	98.7	0.285	C:T
8	rs4713916	35777961	0.393	0.387	0.7322	98.1	0.262	G:A
Check markers suicide								
1	rs3800373	35650454	0.365	0.36	0.7891	98.9	0.235	A:C
2	rs755658	35657648	0.166	0.164	0.9119	95.6	0.09	C:T
3	rs9296158	35675060	0.363	0.369	0.635	98.4	0.244	G:A
4	rs7748266	35700722	0.208	0.223	0.0643	97.2	0.128	C:T
5	rs1360780	35715549	0.365	0.373	0.5708	97.3	0.248	C:T
6	rs9394309	35729759	0.377	0.385	0.5996	96.8	0.26	A:G
7	rs9470080	35754413	0.401	0.399	0.9346	99.0	0.275	C:T
8	rs4713916	35777961	0.372	0.376	0.8302	98.3	0.251	G:A

Abbreviations: *FKBP5*, *FK506 binding protein 5*; SNP, single-nucleotide polymorphism; BP, bipolar disorder; ObsHET, observed heterozygous; PredHET, predicted heterozygous; MAF, minor allele frequency; HWE, Hardy–Weinberg equilibrium; Pos chromos, chromosomal position; zgenotyp, % genotyped (=success rate or call rate).

melancholic depression and not with bipolar patients with psychotic features (shown in Table 3 and Figures 1–3). We did not find any associations with genotypes (data not shown) nor with alleles (shown in Table 4) for the studied polymorphisms.

Discussion

In our study, we found association between haplotypes of the *FKBP5* gene in bipolar patients with suicidal behavior. Since the power for the studied SNPs for our population of bipolar patients was rather low (20%), we assumed that it would be even lower for the subtypes, and due to the small sample we would consider this association as pretty weak. Notwithstanding, our results are in line with previously published associations between haplotypes of the *FKBP5* gene and suicide victims without a history of mental illness at the moment of death.^{3,11} There have also been studies showing associations between polymorphisms of the *FKBP5* gene and suicidal behavior in depressed antidepressant-nonresponding adolescents¹⁷ and childhood trauma victims.¹⁰ Zimmerman et al reported that interaction between the *FKBP5* genotype and trauma is involved in the onset of depression.⁷ Association between the rs1360780 and rs3800373 polymorphisms of the *FKBP5* gene and suicide attempts in Japanese and European populations have been reported.^{11,17}

Table 3 Haplotypes of *FKBP5* gene and subtypes of BP disorder

Haplotype	Freq	Case: control frequencies	Chi-square	P-value
Association-haplotypes melancholic				
ACGCCAC	0.718	0.719, 0.718	0.001	0.9809
CCATTGT	0.117	0.094, 0.121	1.484	0.2232
CTACTGT	0.087	0.100, 0.085	0.624	0.4294
ACGCCGT	0.029	0.031, 0.029	0.038	0.8449
CCACTAT	0.016	0.027, 0.014	2.263	0.1325
CCACTGT	0.012	0.020, 0.011	1.466	0.2261
Association-haplotypes psychotic				
ACGCCAC	0.710	0.679, 0.718	2.193	0.1387
CCATTGT	0.122	0.130, 0.121	0.24	0.6239
CTACTGT	0.087	0.095, 0.085	0.383	0.5362
ACGCCGT	0.031	0.038, 0.029	0.926	0.336
CCACTAT	0.016	0.022, 0.014	1.156	0.2822
Association-haplotypes suicide				
ACGCCAC	0.721	0.736, 0.718	0.429	0.5124
CCATTGT	0.112	0.071, 0.121	6.261	0.0123*
CTACTGT	0.085	0.083, 0.085	0.019	0.8906
ACGCCGT	0.029	0.030, 0.029	0.009	0.9265
CCACTAT	0.018	0.033, 0.014	5.13	0.0235*
CCACTGT	0.013	0.023, 0.011	2.906	0.0883
ACATTGT	0.010	0.016, 0.009	1.166	0.2802

Note: *Indicates association.

Abbreviations: *FKBP5*, *FK506 binding protein 5*; BP, bipolar disorder; Freq, frequency.

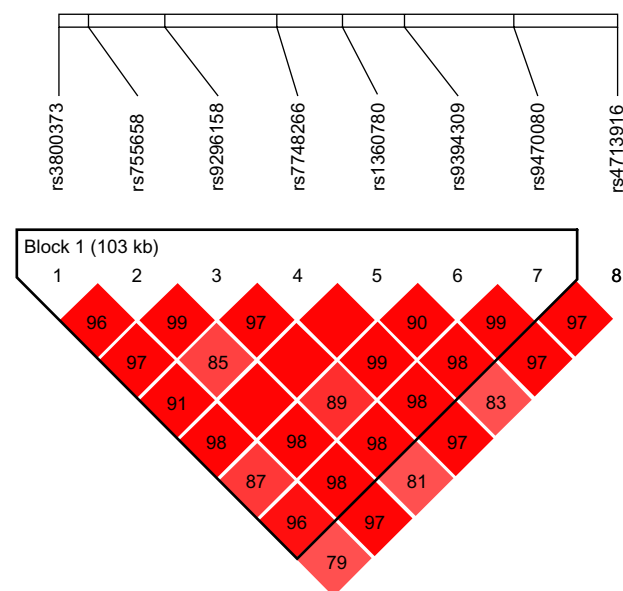


Figure 1 Relative positions and LD estimates between *FKBP5* polymorphisms in the analyzed population-patients with melancholic depression.

Note: Colored squares correspond to D' values with numerical estimates given within the squares.

Associations between variants of the *FKBP5* gene and major depression, bipolar disorder, posttraumatic stress disorder, response to antidepressants, and increased recurrence of depression were also found.^{18–21} There have also been studies showing no associations between polymorphisms of the *FKBP5* gene and depression.²² In the study performed by our group on the same SNPs of the *FKBP5* gene, as in this study, association with major depressive disorder but

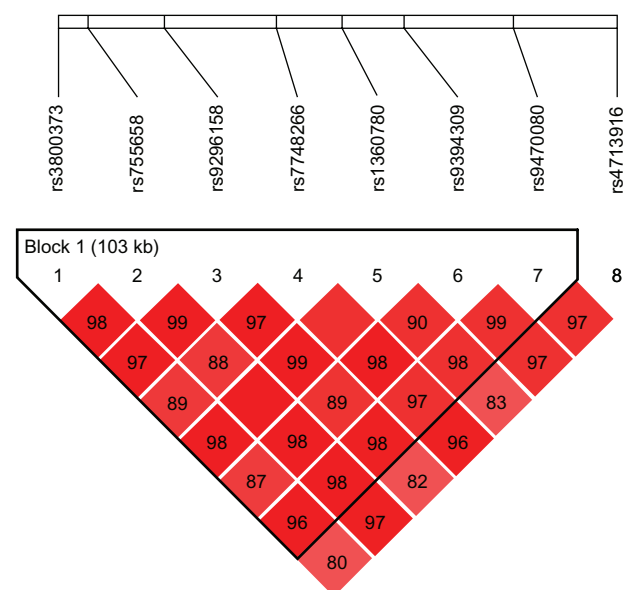


Figure 2 Relative positions and LD estimates between *FKBP5* polymorphisms in the analyzed population-patients with psychotic bipolar disorder.

Note: Colored squares correspond to D' values with numerical estimates given within the squares.

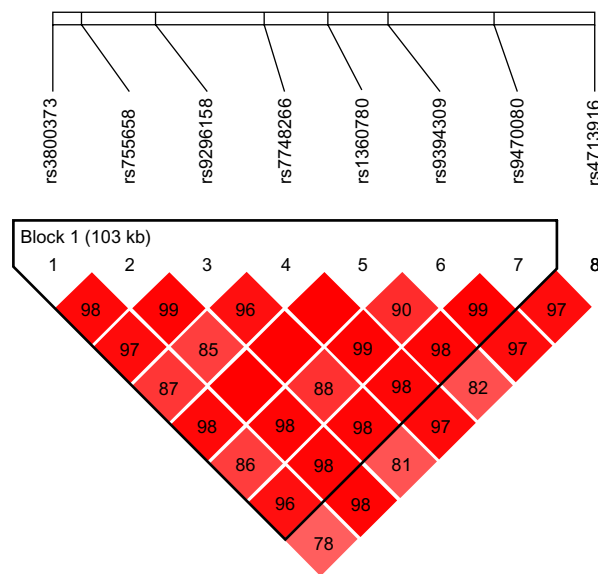


Figure 3 Relative positions and LD estimates between *FKBP5* polymorphisms in the analyzed population-bipolar patients with suicide attempts.

Note: Colored squares correspond to D' values with numerical estimates given within the squares.

not with bipolar disorder was found. It was also proved that clinical differences, such as an increase in previous suicide attempts, are occurring in carriers of the risk allele of the *FKBP5* gene.⁴ One previous study showed male-specific association of the homozygous genotype of the rs1360780 polymorphism;¹⁸ however, other studies have not observed a sex-specific effect of *FKBP5* in psychiatric disorders.^{23,24}

To the best of our knowledge, there have been no studies so far on melancholic depression and psychotic features in the course of bipolar disorder in relation to polymorphisms of the *FKBP5* gene. The lack of association found in the group of melancholic patients is in line with our previously published paper showing no association with the other genes (*NR3C1*, *AVPR1B*, *CRHR1*) involved in the HPA axis.²⁵ Those results are interesting, because it was the melancholic subtype of depression that was strongly correlated with HPA-axis disturbances.

The results showing no association with the *FKBP5* gene and bipolar disorder with psychotic features are also in line with our previous study showing no association with the *NR3C1* gene coding the GR. In the same study, we also proved association between polymorphisms in the *AVPR1B* and *CRHR1* genes and psychotic features in the course of bipolar disorder. In the study performed by Collip et al, which investigated patients with psychotic disorder, their healthy siblings, and controls, an association between trauma and psychosis was apparent. An interaction between the two *FKBP5* SNPs rs9296158 and rs4713916 and childhood trauma in models of psychotic symptoms was found.²⁶ Supporting this hypothesis

Table 4 Alleles for *FKBP5* gene and subtypes of BP disorder

Lp	SNP	Assoc allele	Case: control freq	Chi-square	P-value
Association-alleles melancholic					
1	rs3800373	C	0.244, 0.240	0.017	0.897
2	rs755658	T	0.100, 0.091	0.201	0.6543
3	rs9296158	A	0.250, 0.247	0.008	0.9267
4	rs7748266	C	0.898, 0.865	2.177	0.1401
5	rs1360780	C	0.754, 0.750	0.018	0.8921
6	rs9394309	A	0.760, 0.734	0.727	0.3939
7	rs9470080	T	0.278, 0.277	0.001	0.9744
8	rs4713916	G	0.766, 0.743	0.603	0.4373
Association-alleles psychotic					
1	rs3800373	C	0.262, 0.240	0.764	0.382
2	rs755658	T	0.094, 0.091	0.036	0.8504
3	rs9296158	A	0.271, 0.247	0.896	0.3439
4	rs7748266	T	0.155, 0.135	0.96	0.3271
5	rs1360780	T	0.276, 0.250	1.097	0.295
6	rs9394309	G	0.294, 0.266	1.182	0.2769
7	rs9470080	T	0.319, 0.277	2.627	0.1051
8	rs4713916	A	0.282, 0.257	1.002	0.3168
Association-alleles suicide					
1	rs3800373	A	0.790, 0.760	1.203	0.2728
2	rs755658	C	0.916, 0.909	0.156	0.6924
3	rs9296158	G	0.774, 0.753	0.585	0.4443
4	rs7748266	C	0.907, 0.865	3.905	0.0481*
5	rs1360780	C	0.764, 0.750	0.245	0.6208
6	rs9394309	A	0.767, 0.734	1.35	0.2453
7	rs9470080	C	0.733, 0.723	0.128	0.7202
8	rs4713916	G	0.780, 0.743	1.831	0.176

Note: *Indicates association.

Abbreviations: *FKBP5*, *FK506 binding protein 5*; SNP, single-nucleotide polymorphism; BP, bipolar disorder; Assoc, associated; freq, frequency.

is a study showing that mice lacking the *FKBP5* gene were less vulnerable to the adverse effect of social defeat.²

A possible reason for discrepancies between the results obtained in this study and other results may be different trauma history in each patient, which could lead to epigenetic differences in the *FKBP5* locus and consequently differentiate the genotype effect.²⁷ Another reason for the inconsistent results may be the large degree of linkage disequilibrium in *FKBP5* and the confined knowledge about the functionality of these SNPs.^{26,28,29}

In this context, the main limitation of our study is the absence of data about previous trauma exposure. However, we aimed to examine the narrowly defined phenotype without including environmental interactions. Our study has several other limitations, eg, the fact that 40% of the control group was psychiatrically screened, whereas the remaining control subjects consisted of blood donors that were screened only for somatic disorders; however, taking into account the prevalence of bipolar disorder in the general population, which is about 2%, the risk of involving bipolar disorder patients in the control group is rather low. Another limitation of our study is the small sample size and the low power of the analyzed

SNPs, which of course can lead to false-positive results, so further validation and replication of the present findings is still needed.

In conclusion, the results of our study suggest the involvement of haplotypes of the *FKBP5* gene in the etiology of suicidal behavior, but not in the etiology of melancholic or psychotic features occurring in the course of bipolar illness.

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Disclosure

The authors report no conflicts of interest in this work.

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