Eur Arch Psychiatry Clin Neurosci (2012) 262:305–311
DOI 10.1007/s00406-011-0270-y

ORIGINAL PAPER

Influence of *GRIA1*, *GRIA2* and *GRIA4* polymorphisms on diagnosis and response to treatment in patients with major depressive disorder

Alberto Chiesa · Concetta Crisafulli · Stefano Porcelli · Changsu Han · Ashwin A. Patkar · Soo-Jung Lee · Moon Ho Park · Tae-Youn Jun · Alessandro Serretti · Chi-Un Pae

Received: 3 May 2011 / Accepted: 17 October 2011 / Published online: 5 November 2011

Abstract The present study is aimed to exploring whether some single nucleotide polymorphisms (SNPs) within *GRIA1*, *GRIA2* and *GRIA4* could be associated with major depressive disorder (MDD) and whether they could predict clinical outcomes in Korean in-patients, respectively, treated with antidepressants. One hundred forty-five (145) patients with MDD and 170 healthy controls were genotyped for 17 SNPs within *GRIA1*, *GRIA2* and *GRIA4*. Baseline and final clinical measures, including the Montgomery-Asberg Depression Rating Scale (MADRS) for patients with MDD, were recorded. No association was observed between alleles, genotypes and haplotypes under investigation and clinical and demographical variables. As a secondary finding, a marginal association was observed between rs4302506 and rs4403097 alleles within *GRIA2* and age of onset in patients with MDD. Our findings provide evidence for a possible association between rs4302506 and rs4403097 SNPs and age of onset in patients with MDD. However, taking into account that the several limitations of our study including the moderately small sample size of our study, our findings should be considered with caution and further research is needed to draw more definitive conclusions.

Keywords *GRIA1* · *GRIA2* · *GRIA4* · Major depressive disorder

Electronic supplementary material The online version of this article (doi:10.1007/s00406-011-0270-y) contains supplementary material, which is available to authorized users.

A. Chiesa · S. Porcelli · A. Serretti
Institute of Psychiatry, University of Bologna, Bologna, Italy

C. Crisafulli
Department of Biomorphology and Biotechnologies, Division of Biology and Genetics, University of Messina, Messina, Italy

C. Han
Department of Psychiatry, College of Medicine, Korea University, Ansan, Kyounggi-Do, Republic of Korea

A. A. Patkar · C.-U. Pae
Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA

S.-J. Lee · C.-U. Pae (✉)
Department of Psychiatry, Bucheon St. Mary's Hospital, The Catholic University of Korea College of Medicine, 2 Sosa-Dong, Wonmi-Gu, Bucheon, Kyeonggi-Do 420-717, Republic of Korea
e-mail: pae@catholic.ac.kr

M. H. Park
Department of Neurology, College of Medicine, Korea University, Ansan, Kyounggi-Do, Republic of Korea

T.-Y. Jun
Department of Psychiatry, St. Mary's Hospital, The Catholic University of Korea College of Medicine, Seoul, Republic of Korea

Introduction

Glutamate is the most abundant excitatory neurotransmitter in the brain and it acts by activating two types of receptors: ionotropic receptors (NMDA, AMPA and kainate) and metabotropic receptors ($mGluR_{1-8}$). Current evidence suggests that glutamate plays an important role in several psychiatric conditions, such as schizophrenia, major depressive disorder (MDD) and anxiety disorder [1–5].

AMPA receptors are tetramers comprised of combinatorial assembly of four different subunits referred to as GluR1 (*GRIA1*), GluR2 (*GRIA2*), GluR3 (*GRIA3*) and GluR4, alternatively called GluRA-D2 (*GRIA4*) [6–8].

Different subunits show distinct spatial and temporal distribution in the brain and confer distinct properties to the AMPA receptor complexes [9]. The highest density of AMPA receptors is found in the prefrontal cortex and hippocampus, which are key areas responsible for mood regulation and that are thought to play an important role into the development and maintenance of MDD [10]. Moreover, several studies have indicated that AMPA receptors may be involved into the therapeutic activity of antidepressant drugs [11, 12].

The GluR1 subunit, encoded by *GRIA1* that maps on 5q33, has been shown to influence cognitive function, such as working memory and reward learning [13]. Moreover, ligands to the ionotropic glutamate receptors have demonstrated therapeutic effects in animal models of MDD [14].

GRIA2 encodes for GluR2 and *GRIA4* for GluR4 subunits. Such genes are located on chromosome 4q32–33 and 11q22, respectively. Several studies have suggested the regions spanning the *GRIA2* showed association with major psychiatric disorders such as bipolar disorder and schizophrenia as well as treatment response [15–17]. However, the relationship between *GRIA4* and MDD as well as treatment response is far more limited and less clear thus far.

Overall, current evidence suggests that some *GRIA1*, *GRIA2* and, to a lesser extent, *GRIA4* variants could be associated with some psychiatric disorders as well as with response to their treatments. However, the dearth of studies specifically concerning the relationship between *GRIA1*, *GRIA2* and, particularly, *GRIA4* polymorphisms and MDD suggests the need for further investigation before more definitive conclusions can be drawn. Therefore, the present paper is aimed at investigating whether a set of SNPs within *GRIA1* (rs707176 and rs6875572), *GRIA2* (rs6536221, rs4260586, rs4302506, rs4441804, rs3813296 and rs440 3097) and *GRIA4* (rs11226805, rs2166318, rs11822168, rs1938956, rs10736648, rs528205, rs11226867, rs667174 and rs641574) could be associated with MDD in an independent sample of Korean in-patients. In addition, in the present study we investigated the effects of the same SNPs on clinical improvement in the same samples of MDD patients naturalistically treated with antidepressants.

Methods

Subjects

The sample under investigation in the present study comprised 145 in-patients suffering from MDD who were consecutively recruited at the Department of Psychiatry of the Catholic University of Korea College of Medicine, Seoul, Korea. Patients were eligible for inclusion if they had a documented clinical diagnosis of MDD according to the DSM-IV criteria, as assessed by the Mini-International Neuropsychiatric Interview (M.I.N.I.) [18]. The sample has been previously analyzed regarding other gene variants (e.g., [19]).

There was not any particular restriction with regard to treatments, concomitant comorbidities and first versus following episodes of disease. However, patients were excluded if they had current severe or unstable medical and neurological conditions, current treatment with a long-acting antipsychotic, concomitant alcohol and substance abuse disorders and if they were not of Korean ethnicity. The choice of using not excessively tight inclusion and exclusion criteria was motivated by the decision to include a sample of subjects that could be representative of usual psychiatric in-patients. A further sample of 170 Korean psychiatrically healthy subjects, who underwent the same assessment of psychiatric patients to exclude possible psychiatric disorders, drawn from the same location of the psychiatric patients included in the present study, was also included to compare genotype and allelic frequencies among the three populations of subjects under investigation. Healthy controls included a population sample of healthy donors.

All patients admitted to the hospital were assessed for the severity of illness at baseline and at discharge by means of psychometric questionnaires specific for each disorder under investigation. More in detail, MDD severity was assessed by means of the Montgomery-Asberg Depression Rating Scale (MADRS) [20]. Scorers were trained with the specific instruments with good inter-rater reliability ($k > 0.8$). Additionally, the following clinical and demographic variables were recorded: gender, age, clinical subtypes, age at onset, family history of psychiatric disorders, lifetime suicide attempts, duration of admission, drugs at discharge and use of concomitant anxiolytics. The study protocol was approved by the institutional review board (approval number HC10TISI0031). All patients (18–65 years old) provided written informed consent before participating into the study.

Outcome measures

The main outcomes investigated in the present study were: (1) differences between genotype and allelic frequencies in patients with MDD and healthy control subjects and (2) influences of the SNPs under investigation on clinical improvement in MDD patients mentioned above analyzed separately. Further outcomes of interest comprised the effects of included SNPs on clinical and demographical variables mentioned above as well as on response and remission rates. Both continuous and categorical analyses were performed. In accordance with previous studies,

response was a priori defined as a ≥50% symptoms' reduction from baseline to discharge (e.g., [21]). Remission was defined as a MADRS score ≤7 at discharge for patients with MDD [21].

DNA analysis

Genomic DNA was extracted from blood by standard methods and quantified. The high-throughput genotyping method using pyrosequencer (Biotage AB, Sweden) was used for genotyping 2 SNPs within *GRIA1* (rs707176 and rs6875572), 6 SNPs within *GRIA2* (rs6536221, rs4260586, rs4302506, rs4441804, rs3813296 and rs4403097) and 9 within *GRIA4* (rs11226805, rs2166318, rs11822168, rs1938956, rs10736648, rs528205, rs11226867, rs667174 and rs641574) (Table 1). PCR primers (Bioneer, Daejeon, Korea) and sequencing primers (Bioneer, Daejeon, Korea) used for the pyrosequencing assay were designed by using the Pyrosequencing Assay Design Software v1 (Biotage AB, Sweden), and one primer of each primer set was biotinylated.

Statistical analysis

Statistical analyses were performed using "Statistica" package [22]. Differences in the allelic and genetic frequencies between healthy subjects and patients with MDD as well as effects of such variants on response rates and further categorical outcomes were calculated using the χ^2 statistics. The influence of the SNPs under investigation and continuous outcomes was calculated using the ANOVA. As an example, clinical improvement on MADRS total scores was calculated according to the following formula:

$$[(\mathrm{MADRS}_{\mathrm{final}} - \mathrm{MADRS}_{\mathrm{baseline}})/\mathrm{MADRS}_{\mathrm{baseline}}] \times 100.$$

In case of positive findings, clinical variables correlated with the outcome measures under investigation were added as covariates, so as to investigate possible stratification effects. Haploview 3.2 was used to generate a linkage disequilibrium (LD) map and to test for Hardy–Weinberg equilibrium (HWE) [23]. Tests for associations using multi-marker haplotypes were performed using the statistics environment "R" (http://www.R-project.org), package "haplo.score," to compare clinical and socio-demographic outcomes among different haplotypes. Permutations ($n = 10.000$) were performed to estimate the global significance of the results for all haplotypes analyses.

All *P* values were 2-tailed, and statistical significance was conservatively set at the 0.005 level (corresponding to the Bonferroni correction for the 10 blocks of SNPs under investigation, see below for further information) in order to reduce the likelihood of false-positive results. With these parameters we had a sufficient power (0.80) to detect a small-medium effect size ($\omega = 0.16$) that, as an example, corresponded to an odds ratio of 1.94 between the MDD patients and the group of controls and to detect medium-large (d = 0.29) effect sizes for patients with MDD, carrying the CC genotype of rs4302506 as compared with those carrying the CT genotype [24]. Such effects sizes

Table 1 GRIA1, GRIA2 and GRIA4 SNPs considered in this study

SNP ID	Position[a]	Alleles	Location	Amino-acid exchange
GRIA1				
rs707176	153029960 (159512)	C/T	Coding exon	I → I
rs6875572	153078510 (208062)	A/G	Coding exon	A → A
GRIA2				
rs6536221	158143886 1015	A/G	Intron	None
rs4260586	158157467 14596	A/T	Intron	None
rs4302506	158238830 95959	C/T	Coding exon	H → H
rs4441804	158267535 124664	C/T	Intron	None
rs3813296	158281523 138652	G/T	Intron	None
rs4403097	158285597 142726	C/T	3′-UTR	None
GRIA4				
rs11226805	105482024 300	C/T	Intron	None
rs2166318	105483661 1937	A/G	Intron	None
rs11822168	105630803 149079	A/G	Intron	None
rs1938956	105640104 158380	G/T	Intron	None
rs10736648	105642936 161212	A/G	Intron	None
rs528205	105719522 237798	G/T	Intron	None
rs11226867	105734327 252603	A/G	Intron	None
rs667174	105753035 271311	C/T	Intron	None
rs641574	105812839 331115	A/G	Intron	None

[a] Absolute chromosomal position. The relative position to the start codon is given in parenthesis. All data from http://www.snpper.chip.org. *I* isoleucine, *A* alanine, *H* Histidine

corresponded to the possibility of detecting final differences on MADRS of 4 points.

Results

Socio-demographic features of MDD patients and controls

Socio-demographic features of patients with MDD are reported in Table 2. For control subjects, only data about gender and age were collected (see [19]). There were no significant differences among the two groups with regard to age and gender (gender: $P = 0.09$; age: $P = 0.09$). There were no associations between any of the SNPs under investigation and baseline clinical variables (all P values >0.05).

Hardy–weinberg equilibrium (HWE) and linkage disequilibrium for GRIA1, GRIA2 and GRIA4 SNPs

Two out of 19 SNPs under investigation were not polymorphic in the present sample (rs6875572 and rs6536221 in *GRIA1* and *GRIA2*, respectively) and were therefore excluded from the analyses. The remaining SNPs were all in HWE in the whole sample (rs707176: $P = 1.0$, rs4260586: $P = 0.79$; rs4302506: $P = 0.80$, rs4441804: $P = 0.57$, rs3813296: $P = 0.44$, rs11226805: $P = 0.63$, rs2166318: $P = 0.28$, rs11822168: $P = 0.13$, rs1938956: $P = 0.25$, rs10736648: $P = 0.50$, rs528205: $P = 0.46$, rs11226867: $P = 0.32$, rs667174: $P = 0.99$, rs641574: $P = 0.76$). Strong LD was observable between rs4260586, rs4302506, rs4441804, rs3813296 and rs4403097 within *GRIA1* and between rs11226805, rs2166318 and rs11822168, between rs1938956, rs10736648 and rs528205 and between rs11226867, rs667174 and rs641574 within *GRIA4*; see Figs. 1, 2). Patients and healthy controls separately analyzed yielded similar results (data not shown).

Differences between genotype and allelic frequencies in MDD patients and healthy controls

There were no significant differences between allelic and genotype frequencies in MDD patients and healthy controls (online Table 1; all P values >0.005).

Influence of GRIA1, GRIA2 and GRIA4 variants on clinical improvement in MDD patients

We did not observe any association between the genetic variants under investigation in the present study and MADRS total scores in patients with MDD (online

Table 2 Clinical and demographic characteristics of the sample

Clinical and demographic characteristics	Major depressive disorder ($n = 145$)
Gender	
Males	75 (52%)
Females	70 (48%)
Age	41.37 ± 14.07
MADRS	
Baseline	34.35 ± 8.95
Discharge	17.12 ± 9.88
Response	
Yes	78 (54%)
No	66 (45%)
Missing	1 (1%)
Remission	
Yes	22 (15%)
No	122 (84%)
Missing	1 (1%)
Clinical subtypes	
MDD without PF	105 (72%)
MDD with PF	11 (8%)
Dysthymia	4 (3%)
MDD NOSs	5 (4%)
Missing value	20 (13%)
Age at onset	38.08 ± 13.29
Family history of psychiatric disorders	
Yes	30 (21%)
No	92 (63%)
Missing values	23 (16%)
Suicide attempts	
Yes	36 (25%)
No	92 (63%)
Missing value	17 (12%)
Duration of admission (days)	32.31 ± 20.55
Drug	
Paroxetine	40 (27%)
Venlafaxine	35 (24%)
Fluoxetine	23 (16%)
Mirtazapine	21 (14%)
Other	3 (3%)
Missing value	23 (16%)
Concomitant anxiolytics	
Alprazolam	30 (21%)
Lorazepam	73 (50%)
Clonazepam	3 (2%)
Buspiron	4 (3%)
None	35 (24%)

MADRS Montgomery-Asberg Depression Rating Scale, *PF* psychotic feature, *MDD* major depressive disorder, *NOS* not otherwise specified

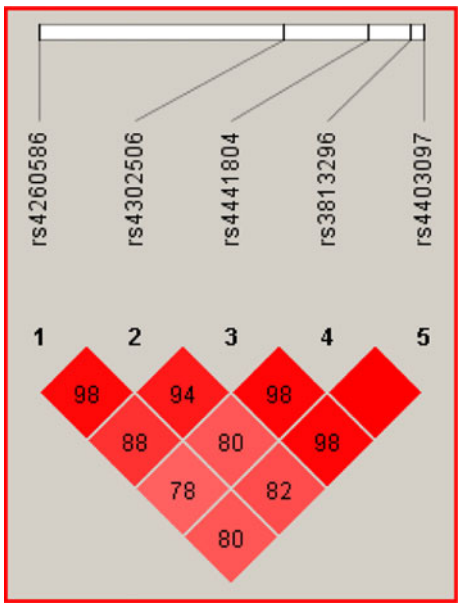

Fig. 1 Linkage disequilibrium of *GRIA2* SNPs under investigation in the present study

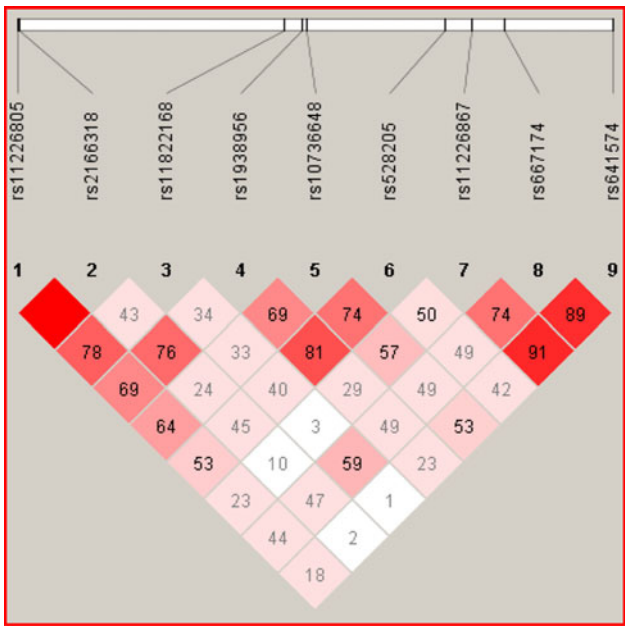

Fig. 2 Linkage disequilibrium of *GRIA4* SNPs under investigation in the present study

Table 2; all P values >0.005). The haplotype analysis focusing on the sliding windows haplotypes mentioned above did not find any significant association as well. Consideration of treatment as covariant did not influence results.

Influence of GRIA1, GRIA2 and GRIA4 variants on further clinical and socio-demographical variables in patients with MDD

Marginal associations were observed between rs4302506 and rs4403097 alleles within *GRIA2* and age of onset in patients with MDD. More in detail, the rs4302506 C allele and the rs4403097 T allele were associated with a lower age of onset of MDD ($F = 8.85$, d.f. = 1,260, $P = 0.003$ and $F = 7.84$, d.f. = 1,260, $P = 0.005$, respectively). Of note, a trend toward significance between rs4302506 and age of onset in MDD was observed in the genotype analysis as well. Indeed, subjects carrying the rs4302506 CC genotype had a slightly significant lower age of onset of MDD as compared with those carrying the TC and the TT genotypes ($F = 5.14$, d.f. = 2,128, $P = 0.007$, see online Table 2).

No further association was observed between the remaining alleles and genotypes under investigation and clinical and demographical variables. Response rates did not significantly differ across different genotypes as well (online Table 3). Furthermore, none of the haplotypes under investigation was associated with any of such measures.

Discussion

The present paper was aimed at exploring whether specific SNPs within *GRIA1*, *GRIA2* and *GRIA4* could be associated with MDD and whether the same variants could predict clinical outcomes. In addition, we explored whether such variants could be associated with several clinical and socio-demographical variables of our sample.

First of all, our results suggest that the rs4302506 and rs4403097 alleles within *GRIA2* could be associated with age of onset in patients with MDD. In particular, we found an association between rs4302506 C allele and the rs4403097 T allele and lower age of onset of MDD. Moreover, a trend toward significance between rs4302506 and age of onset in MDD was observed in the genotype analysis as well. Indeed, subjects carrying the rs4302506 CC genotype had a significantly lower age of onset of MDD as compared with those carrying the TC and the TT genotypes. In spite of the dearth of studies specifically dealing with the present topic, these findings are in line with the notion that early onset of disease could be a key indicator for a heritable form of MDD [25].

We found no significant differences between allelic and genotype frequencies in MDD patients and healthy controls. Possible explanations for the negative findings could be imputed to differences in terms of ethnicity, study design and SNPs under investigation. Note also that, although Kerner et al. [26] consistently found associations between *GRIA1* SNPs and psychotic bipolar disorder, no individual SNP could be replicated across datasets.

Moreover, we did not observe any significant association between the genetic variants under investigation and clinical improvement in patients with MDD, and the haplotype analysis focusing on the sliding windows haplotypes mentioned above did not find any significant association as well. Of note, while current evidence suggests that some *GRIA1*, *GRIA2* and *GRIA4* variants could be associated with several psychiatric disorders as well as with response to their treatments, the majority of current evidence focused on schizophrenia and little is known about the relationship between these genes variants and MDD thus far. Therefore, we could preliminarily suggest that genetic variants under investigation in the present study could be either not associated with MDD as well as with response to their treatments or more specifically associated with some domains, such as cognition or affectivity, that could indirectly affect the development and response to treatment of such disorders.

Before firm conclusions are drawn, however, several limitations of the present study should be carefully considered. First of all, as reported above, candidate genetic studies such as the present one are associated with a high likelihood of false-positive findings [27]. On the other hand, negative results could be related to the lack of statistical power that could obscure small effects exerted by single SNPs. Recently, odds ratios of less than 1.4 were reported, below our detectable threshold. A further concern is related to the use of several drugs with different mechanisms of action for each cohort of patients that does not allow to draw definitive conclusions with regard to the influence of the SNPs under investigation on specific drugs or classes of drugs. However, our decision to include patients treated with different drugs could have the advantage of being closer to "real world" clinical practice, and consideration of this variable did not affect results. Also, the duration of hospitalization in the present study could be considered as insufficient to ascertain a lack of response and remission, though this time frame is consistent with common clinical practice [28]. Furthermore, other dimensions of clinical improvement might be influenced by the SNPs under investigation other than depressive symptoms. However, we collected only such information. A further limitation of this study could be related to the incomplete coverage of genes under investigation, due to our tagging approach. Finally, we obtained only limited information about some clinical and socio-demographical variables in patients with MDD, and it is therefore unclear whether additional information could have altered our results.

In conclusion, our results suggest that rs4302506 and rs4403097 SNPs could be associated with age of onset in patients with MDD. However, taking into account the limitations of the present study, our findings should be considered with caution and replications in larger sample of patients treated with more standardized pharmacological regimens are needed to draw more definitive conclusions.

Acknowledgment This study was supported by a grant of the Korean Healthcare technology R&D Project, Ministry of Health and Welfare, Republic of Korea (A102065).

Conflict of interest None.

References

1. Danysz W, Parsons CG (1998) Glycine and n-methyl-d-aspartate receptors: physiological significance and possible therapeutic applications. Pharmacol Rev 50:597–664
2. Preskorn SH, Baker B, Kolluri S, Menniti FS, Krams M, Landen JW (2008) An innovative design to establish proof of concept of the antidepressant effects of the nr2b subunit selective n-methyl-d-aspartate antagonist, cp-101, 606, in patients with treatment-refractory major depressive disorder. J Clin Psychopharmacol 28:631–637
3. Martins-de-Souza D, Harris LW, Guest PC, Turck CW, Bahn S (2010) The role of proteomics in depression research. Eur Arch Psychiatry Clin Neurosci 260:499–506
4. Wang X, Li YH, Li MH, Lu J, Zhao JG, Sun XJ, Zhang B, Ye JL (2011) Glutamate level detection by magnetic resonance spectroscopy in patients with post-stroke depression. Eur Arch Psychiatry Clin Neurosci. doi: 10.1007/s00406-011-0209-3
5. Schmitt A, Hasan A, Gruber O, Falkai P (2011) Schizophrenia as a disorder of disconnectivity. Eur Arch Psychiatry Clin Neurosci. doi: 10.1007/s00406-011-0242-2
6. Nakanishi N, Shneider NA, Axel R (1990) A family of glutamate receptor genes: evidence for the formation of heteromultimeric receptors with distinct channel properties. Neuron 5:569–581
7. Wenthold RJ, Yokotani N, Doi K, Wada K (1992) Immunochemical characterization of the non-nmda glutamate receptor using subunit-specific antibodies. Evidence for a hetero-oligomeric structure in rat brain. J Biol Chem 267:501–507
8. Wenthold RJ, Petralia RS, Blahos J II, Niedzielski AS (1996) Evidence for multiple ampa receptor complexes in hippocampal ca1/ca2 neurons. J Neurosci 16:1982–1989
9. Hollmann M, Hartley M, Heinemann S (1991) $Ca2^{+}$ permeability of ka-ampa–gated glutamate receptor channels depends on subunit composition. Science 252:851–853
10. Bleakman D, Alt A, Witkin JM (2007) Ampa receptors in the therapeutic management of depression. CNS Neurol Disord Drug Targets 6:117–126
11. Martinez-Turrillas R, Del Rio J, Frechilla D (2005) Sequential changes in bdnf mrna expression and synaptic levels of ampa receptor subunits in rat hippocampus after chronic antidepressant treatment. Neuropharmacology 49:1178–1188
12. Palucha A, Pilc A (2007) Metabotropic glutamate receptor ligands as possible anxiolytic and antidepressant drugs. Pharmacol Ther 115:116–147
13. Schmitt WB, Sprengel R, Mack V, Draft RW, Seeburg PH, Deacon RM, Rawlins JN, Bannerman DM (2005) Restoration of spatial working memory by genetic rescue of glur-a-deficient mice. Nat Neurosci 8:270–272
14. Black MD (2005) Therapeutic potential of positive ampa modulators and their relationship to ampa receptor subunits. A review of preclinical data. Psychopharmacology (Berl) 179:154–163
15. Ekholm JM, Kieseppa T, Hiekkalinna T, Partonen T, Paunio T, Perola M, Ekelund J, Lonnqvist J, Pekkarinen-Ijas P, Peltonen L

(2003) Evidence of susceptibility loci on 4q32 and 16p12 for bipolar disorder. Hum Mol Genet 12:1907–1915
16. McInnis MG, Lan TH, Willour VL, McMahon FJ, Simpson SG, Addington AM, MacKinnon DF, Potash JB, Mahoney AT, Chellis J, Huo Y, Swift-Scanlan T, Chen H, Koskela R, Stine OC, Jamison KR, Holmans P, Folstein SE, Ranade K, Friddle C, Botstein D, Marr T, Beaty TH, Zandi P, DePaulo JR (2003) Genome-wide scan of bipolar disorder in 65 pedigrees: supportive evidence for linkage at 8q24, 18q22, 4q32, 2p12, and 13q12. Mol Psychiatry 8:288–298
17. Hovatta I, Varilo T, Suvisaari J, Terwilliger JD, Ollikainen V, Arajarvi R, Juvonen H, Kokko-Sahin ML, Vaisanen L, Mannila H, Lonnqvist J, Peltonen L (1999) A genomewide screen for schizophrenia genes in an isolated finnish subpopulation, suggesting multiple susceptibility loci. Am J Hum Genet 65:1114–1124
18. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC (1998) The mini-international neuropsychiatric interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for dsm-iv and icd-10. J Clin Psychiatry 59(Suppl 20):22–33 (quiz 34–57)
19. Serretti A, Chiesa A, Porcelli S, Han C, Patkar AA, Lee SJ, Park MH, Pae CU (2011) Influence of tph2 variants on diagnosis and response to treatment in patients with major depression, bipolar disorder and schizophrenia. Psychiatry Res 189:26–32
20. Montgomery SM (1979) Depressive symptoms in acute schizophrenia. Prog Neuropsychopharmacol 3:429–433
21. Riedel M, Moller HJ, Obermeier M, Schennach-Wolff R, Bauer M, Adli M, Kronmuller K, Nickel T, Brieger P, Laux G, Bender W, Heuser I, Zeiler J, Gaebel W, Seemuller F (2010) Response and remission criteria in major depression–a validation of current practice. J Psychiatr Res 44:1063–1068
22. StatSoft (1995) Statistica per windows. StatSoft Italia srl
23. Barrett JC, Fry B, Maller J, Daly MJ (2005) Haploview: analysis and visualization of ld and haplotype maps. Bioinformatics 21:263–265
24. Cohen J (1988) Statistical power analysis for the behavioral sciences. Lawrence Erlbaum Associates, Hillsdale, pp 8–14
25. Zubenko GS, Zubenko WN, Spiker DG, Giles DE, Kaplan BB (2001) Malignancy of recurrent, early-onset major depression: a family study. Am J Med Genet 105:690–699
26. Kerner B, Jasinska AJ, DeYoung J, Almonte M, Choi OW, Freimer NB (2009) Polymorphisms in the gria1 gene region in psychotic bipolar disorder. Am J Med Genet B Neuropsychiatr Genet 150B:24–32
27. Sullivan PF (2007) Spurious genetic associations. Biol Psychiatry 61:1121–1126
28. Zimmerman M, Mattia JI, Posternak MA (2002) Are subjects in pharmacological treatment trials of depression representative of patients in routine clinical practice? Am J Psychiatry 159:469–473