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A genome-wide association study points to multiple loci predicting antidepressant treatment outcome in depression

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Abstract

Context—Efficacy of antidepressant treatment in depression is unsatisfactory as one in three patients does not fully recover even after several treatment trials. Genetic factors and clinical characteristics contribute to the failure of a favorable treatment outcome.

Objective—To identify genetic and clinical determinants of antidepressant treatment outcome in depression.

Design—Genome-wide pharmacogenetic association study with two independent replication samples.

Setting—We performed a genome-wide association (GWA) study in patients from the Munich-Antidepressant-Response-Signature (MARS) project and in pooled DNA from an independent German replication sample. A set of 328 single nucleotide polymorphisms (SNPs) highly related

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to outcome in both GWA studies was genotyped in a sample of the Sequenced-Treatment-Alternatives-to-Relieve-Depression (STAR*D) study.

Participants—339 inpatients suffering from a depressive episode (MARS sample), further 361 depressed inpatients (German replication sample), and 832 outpatients with major depression (STAR*D sample).

Main Outcome Measures—We generated a multi-locus genetic variable describing the individual number of alleles of the selected SNPs associated with beneficial treatment outcome in the MARS sample ("response" alleles) to evaluate additive genetic effects on antidepressant treatment outcome.

Results—Multi-locus analysis revealed a significant contribution of a binary variable categorizing patients as carriers of a high vs. low number of response alleles in predicting antidepressant treatment outcome in both samples, MARS and STAR*D. In addition, we observed that patients with a comorbid anxiety disorder in combination with a low number of response alleles showed the least favorable outcome.

Conclusion—Our results demonstrate the importance of multiple genetic factors in combination with clinical features to predict antidepressant treatment outcome underscoring the multifactorial nature of this trait.

Antidepressants are indispensable in treating severe depression. Since their discovery in the 1950s, side-effect profiles of these drugs have been improved, while clinical efficacy is still unsatisfactory as one in three patients does not fully recover from depression, even after several treatment trials.[1,2] Genetic factors contribute to the general variability in drug response[3,4] and according to family studies this is also the case for antidepressants,[5-7] suggesting that the individual genetic profile may provide guidance in medication selection.[8] Up to now, pharmacogenetic studies have been focused on candidate genes implicated in the mechanisms of antidepressant drug action or in the pharmacokinetics of such drugs. For example, an insertion/deletion polymorphism in the promoter region of the serotonin transporter (SLC6A4) gene seems to predict response to selective serotonin reuptake inhibitors (SSRIs),[9] potentially mediated by differences in SSRI tolerability,[10] and a variation in the ABCB1 gene coding for a P-glycoprotein that determines brain tissue penetration of many antidepressants may predict clinical outcome of patients treated with substrates of this blood brain barrier regulation molecule.[11] Several studies reported that variants of a gene coding for FKBP5,[12-14] a co-chaperone involved in stress hormone signaling, and for 5HT2A,[15] are predictive of treatment response, but do not effectively guide treatment selection. Further associations have been reported for the glutamatergic receptor gene GRIK4,[16] the enzymatic gene PDER11A,[17] inflammation related genes (CD3E, PRKCH, PSMD9, and STAT3),[18] and for UCN3[18] expressing a ligand of the CRF2 receptor.

As the mechanisms by which antidepressants exert their clinical effects are yet not fully understood, studies focusing on single candidate genes may fail to identify novel genetic information of clinical importance. Therefore, we conducted an unbiased genome-wide pharmacogenetic study in patients under antidepressant treatment to discover new gene variants that contribute to a favorable outcome. Furthermore, treatment response is not only

determined by genetic makeup but also by course of illness, comorbid anxiety, age at disease onset, current age or gender.[1,19,20] These variables were additionally considered whether they predict the outcome of antidepressant treatment.

Methods

We report the results of two genome-wide association (GWA) studies. In the first study, we genotyped patients from the Munich-Antidepressant-Response-Signature (MARS) project;[1] in the second study, we determined genome-wide allele frequencies in pooled DNA from a German replication sample. Subsequently, a set of single nucleotide polymorphisms (SNPs) highly related to outcome in both GWA studies was genotyped in a sample from the Sequenced-Treatment-Alternatives-to-Relieve-Depression (STAR*D) study[2] - a multicenter treatment trial using a series of standard treatments in an outpatients sample. We were encouraged to use MARS and STAR*D as discovery and replication samples, because several concordant pharmacogenetic findings in candidate gene studies emerged from both.[12,14,15]

MARS sample

339 Caucasian inpatients from the MARS project[1] suffering from a major depression (88.8%) or bipolar disorder (11.2%; see Table 1) were included within 1-5 days following admission as inpatients. Diagnosis was ascertained by trained psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria. Exclusion criteria were presence of alcohol/substance abuse or dependence (including eating disorders with concomitant laxative abuse), comorbid somatization disorder as well as depressive disorders due to general medical or neurological conditions. Ethnicity was recorded using a self-report questionnaire asking for nationality, first language and ethnicity of the subject and all 4 grandparents. All patients were Caucasian and 85.1% were of German descent, the remaining patients of European descent (Central Europe: 6.5%; Eastern Europe: 7.8%; Mediterranean: 0.6%). The study was approved by the local ethics committee of the Ludwig Maximilians University of Munich, and written informed consent was obtained from all participants.

Severity of psychopathology was assessed by trained raters using the 21-item Hamilton Depression Rating Scale (HAM-D).[21] Patients with at least moderately severe depression (HAM-D ≥ 14) entered analysis. Ratings were performed within 3 days of admission and then weekly until discharge. We used three common types of response definitions, each defining different aspects of antidepressant treatment outcome: early partial response (HAM-D reduction of at least 25% after two weeks of treatment), response (HAM-D reduction of at least 50% after five weeks of treatment), and remission (HAM-D score of less than 10, evaluated after five weeks and prior to discharge from hospital). The MARS project was designed as a naturalistic pharmacogenetic study, where all patients were treated with antidepressants according to doctor's choice; plasma antidepressant concentrations were monitored to assure clinically efficient drug levels.

German inpatient replication sample

The German replication sample consisted of 361 Caucasian inpatients from the psychiatric hospital of the Ludwig Maximilians University (LMU), Munich, and from the psychiatric hospital of the University of Münster. Gender distribution ($p>.2$) and age ($p>.9$) did not differ between samples. Overall, 85% of these patients suffered from major depression, while 15% were in a depressive episode of a bipolar disorder. Trained psychiatrists ascertained DSM IV diagnosis. Patients were rated weekly from admission to discharge (Munich) or until week 6 (Münster) using the 21-item HAM-D rating scale. Ethnicity was recorded using the same self-report questionnaire as in the MARS study. All patients were Caucasian and 90.7% were of German origin; the remaining patients were of European descent (Central Europe: 3.9%; Eastern Europe: 5.3%; Mediterranean: 0.1%). Same inclusion/exclusion criteria applied as in the MARS sample, and outcome under antidepressant treatment was evaluated accordingly.

STAR*D replication sample

A subsample of 832 outpatients from the STAR*D study[20,22] was selected as second replication sample. Selection criteria were Caucasian ethnicity, a score equal or larger than 10 in the 16 items clinician rating version of the Quick Inventory of Depressive Symptomatology (QIDS-C)[23] at time of study inclusion (corresponding to a HAM-D score ≥ 14), and availability of QIDS-C data for at least the first two weeks of treatment. In agreement with the selection criteria of the MARS study and the German replication sample, patients with concurrent alcohol or substance use disorder, bulimia, and somatization disorder diagnosed with the Psychiatric Diagnostic Screening Questionnaire[24] were excluded. In addition, 12 subjects were excluded due to low genotyping quality. All patients participated in the first treatment step (level 1) of the STAR*D study and received citalopram. To identify partial response, response and remission in a manner consistent with the two German studies, we selected QIDS-C scores that corresponded to the HAM-D scores used in the initial samples following published conversion recommendations.[23] For demographic and clinical characteristics of this STAR*D sample, see Table 1.

Control subjects for the case/control analysis

A total of 366 control subjects (161 males, 205 females, age 48.6±13.4) matched to the MARS sample for ethnicity (using the same questionnaire), gender and age were recruited at the Max Planck Institute of Psychiatry. They were selected randomly from a Munich-based community sample. Exclusion criteria were presence of severe somatic diseases and a lifetime history of Axis I mental disorders. The latter was ascertained using the Munich version of the Composite International Diagnostic Interview (M-CIDI).[25]

SNP genotyping

Genotyping in the MARS sample was performed using two types of whole-genome genotyping arrays, the Illumina Sentrix Human-1 (109k) and HumanHap300 (317k) beadchip (Illumina Inc., San Diego, USA), which together covered almost 410,000 non-overlapping SNPs from the entire human genome. Genotyping was performed according to

the manufacturer's standard protocols. We excluded all SNPs with a call rate of less than 98%, with a deviation from Hardy-Weinberg equilibrium (HWE) at an error level of $<10^{-5}$, or with a minor allele frequency (MAF) <2.5%, resulting in 93,339 SNPs from the Human-1 and 295,912 SNPs from the HumanHap300 chip. 4.5% of all analyzed SNPs showed a nominally significant deviation from HWE with the level of significance set to 5%, which is almost identical to the expected number of false positive findings under the null hypothesis of missing HWE deviations (p=.832). The average case-wise call rate across all SNPs was 99.8%, and the reproducibility for samples (n=3) genotyped twice was 99.999%. A test for population stratification with 10,000 random SNPs as genomic controls showed no evidence for admixture.

Genome-wide allele frequencies in the German replication sample were determined separately in three pairs of pools containing the DNA of patients with i) early partial response vs. non-response, ii) response after 5 weeks vs. non-response, and iii) remission after five weeks vs. non-remission. DNA of responders after 5 weeks was pipetted in duplicate for reasons of quality control. Due to technical restrictions, genome-wide analysis of the pooled DNAs was performed only with the Illumina HumanHap300 (317k) BeadChip. All pools were measured three times, except the duplicated DNA pools of 5 weeks responders that were measured twice. Allele frequencies were estimated from the intensity scores obtained from all 19 pool assessments using BeadStudio software (ver. 3.1.00; Illumina Inc., San Diego, USA). This method was recently proved valid in several studies including case/control studies in late-onset Alzheimer's disease[26] and in schizophrenia[27], and a comparison with individual genotyping revealed excellent concordance for the Illumina HumanHap300 array.[28] A proximity analysis of our data revealed a perfect clustering of the estimated allele frequencies of the 19 pools resulting in separate clusters for the 6 phenotypes (early partial response/non-response, response/non-response after 5 weeks, remission/non-remission after 5 weeks). The average MAF correlation across pools was .98, and the correlation with the individual allele frequencies from the CEU sample of the HapMap project (http://www.hapmap.org) was .93, matching the result of another European genome-wide association study using Illumina HumanHap arrays with pooled DNA (r=.94).[27]

We selected 338 SNPs for replication in the STAR*D sample. The selection criteria were the “best” 300 SNPs from the HumanHap300 chip (corresponding to 1 ‰) showing concordant associations with treatment outcome in both genome wide samples with the lowest combined p-values (geometric mean of the respective p-values) plus 38 SNPs from the Human-1 chip associated with treatment outcome in the MARS sample achieving a p-value below 1×10^{-4}. Of these SNPs, 328 could be successfully genotyped using a GoldenGate custom assay (Illumina Inc., San Diego, USA) with a call rate of larger than 98%. 4.9% of these SNPs showed a nominally significant deviation from HWE at a level of significance of 5% corresponding to the expected number of false positive findings under the null hypothesis of no HWE deviation (p=.964). Average MAF was 27% ranging from 7% to 49.9% with more than 80% of the SNPs showing a MAF larger than 15%.

Power calculation

Power calculation was conducted using the CaTS Power Calculator for Genome Wide Association Studies[29]. Applying a two-stage design with genome-wide scans as the first stage and a replication of 328 genotypes as the second stage, we calculated a power of 80% to detect genetic effects (allelic model) with a relative risk of 1.60 for SNPs with a minor allele frequency of at least 15% and under the assumption of 33% favorable treatment outcome.

Statistics

Pharmacogenetic analyses were conducted using chi-square statistics. Treatment outcome was evaluated binary as partial response after two weeks, response and remission after five weeks. A genotypic (MARS) and allelic model (MARS, German replication sample, STAR*D) was calculated. To reduce false-positive results, we corrected for multiple comparisons using a re-sampling method with N=10,000 permutations following the approach by Westfall and Young,[30] which considers the dependence structure of the genotypes to control for an irregular increase of the beta error.

In addition, a multi-locus survival analysis was performed in the MARS and the STAR*D sample. For this analysis, “response alleles” were determined according to the results of the MARS study for each of the 328 SNPs considered for replication in the STAR*D sample. For 18 SNPs, response alleles could not be unambiguously identified; these SNPs were omitted from the multi-locus analysis. We calculated a second score after weighting the number of alleles with the respective odds ratio from the MARS sample. Cox regression modeling was applied using a proportional hazard function for occurrence and time until remission during the first eight weeks of treatment. Missing HAM-D and QIDS-C scores were estimated using non-linear regression to benefit from a complete data set, and HAM-D values from the MARS sample were translated into equivalent QIDS-C scores. Assuming that a certain threshold of risk alleles may be required to predict an unfavorable outcome, we defined a threshold model of multiple genetic influences. Patients were categorized as high or low response allele carriers according to their additive and weighted response allele score, respectively. In addition, clinical predictors for treatment outcome including age at onset, diagnosis of recurrent depression, chronic depression, or of a comorbid anxiety disorder (general anxiety disorder, panic disorder, social phobia) as well as age and gender were considered in the Cox regression model. According to previous results of the MARS and STAR*D study, we assumed beneficial effects on treatment outcome for female gender,[20] young age,[31] late age at onset,[31,32] absence of recurrent[33] and chronic depression episodes,[31,34] or comorbid anxiety disorders[1,19,20]. We further assumed favorable effects for a high number of response alleles. One-sided p-values according to the prediction hypotheses are reported.

Pathway analysis

A pathway analysis of genes corresponding to the SNPs selected for replication in the STAR*D sample was performed with Genomatix BiblioSphere Pathway Edition (Version 7.16; http://www.genomatix.de/products/BiblioSphere/). BiblioSphere Pathway Edition is a

heuristic method to summarize available evidence about gene relationships by systematically extracting and analyzing scientific databases. These databases are NCBI PubMed, NCBI Entrez Gene, and Genomatix MatBase, a comprehensive transcription factor data base. Genes were categorized as related if co-cited in the same sentence of an abstract with a functional descriptor in-between (evidence level B3). Gene clusters were identified according to the number of co-citations of each pair of genes.

Results

Genome-wide association analysis

In accordance with our previous pharmacogenetic studies,[11,12] we evaluated early partial response (HAM-D reduction of at least 25%) after two weeks, response (HAM-D reduction of at least 50%) and remission (HAM-D score of less than 10) after five weeks as antidepressant outcome phenotypes: The genome-wide results for the MARS sample are presented in Figure 1, showing the effect of the outcome phenotype with the highest genotypic or allelic association. The largest pharmacogenetic association was found for rs6989467 (early partial response, genotypic model, $p=7.6\times10^{-7}$, see Fig. 1), which is located in the 5' flanking region to the CDH17 gene on 8q22; several other associations with a nominal p-value below 1×10^{-5} were found. Using the multivariate Fisher-Product Method (geometric mean of the p-values) across the three outcome phenotypes, the strongest effect was observed for rs1502174 (dominant-recessive model, $p=8.5\times10^{-5}$) located in the 3' flanking region of the EPHB1 gene on 3q22. However, no effect withstood correction for multiple testing.

Before testing replication in the STAR*D sample, we performed another GWA using pooled DNA from an independent German sample of depressed inpatients. This analysis aimed to identify genotypes concordantly associated with treatment outcome in both samples to reduce the likelihood of false positive results. The effects observed in the pooled sample were within a somewhat smaller range of p-values with the highest association found for rs1912674 (early partial response, $p=8.9\times10^{-7}$) located in the region between the AK090788 and PDE10A genes on 6q21. No effect remained significant after correction for multiple testing.

STAR*D replication sample

For the replication analysis in the STAR*D sample, we selected 300 SNPs from the Illumina Sentrix HumanHap300 chip showing concordant allelic associations with treatment outcome in both German samples with the lowest combined p-values. In addition, 38 SNPs from the Illumina Sentrix Human-1 chip with the lowest p-values in the MARS sample were selected. Of these SNPs, 328 were successfully genotyped using an Illumina GoldenGate custom assay (see eTable, Supplementary Online Content). The genotypes of these SNPs did not differ between patients (MARS) and a sample of healthy controls matched for age, gender, and ethnicity after correction for multiple testing ($p_{corrected}>.5$). When evaluating associations with treatment outcome in the STAR*D sample (partial response after two weeks, response/remission after five weeks, remission at the end of the first treatment period), 46 SNPs were associated at the nominal level of significance ($p_{nominal}<.05$)

showing allelic effects in the same direction as in the MARS sample and the German replication sample (see eTable, Supplementary Online Content, highlighted entries). These effects, however, did not withstand correction for multiple testing ($p_{corrected}>.1$).

Multi-locus analysis

Next, we investigated whether the prediction of treatment outcome could be improved if multiple allelic effects were considered simultaneously in combination with clinical variables. For this purpose, we generated a multi-locus genetic variable describing the individual number of alleles associated with beneficial treatment outcome in the MARS sample, assuming an additive effect of the 328 selected SNPs. For 18 SNPs, response alleles could not be unambiguously identified, as only the heterogeneous genotype (presence of both alleles) was associated with favorable treatment outcome. These SNPs were omitted from the multi-locus analysis.

We used a survival analytical approach evaluating the occurrence of remission during the first eight weeks of treatment, which is the minimal time-period recommended for clinical studies with remission as primary outcome.[35] Age, gender, age at onset, recurrence of episodes, chronic episode (≥ 2 years), comorbid anxiety disorder as well as the response allele score were included to predict remission during the first eight weeks of treatment (Table 2a).

Consistent for both samples, MARS and STAR*D, and for the combined analysis, the survival analysis demonstrated a negative effect of comorbid anxiety disorder as well as a positive effect of the number of response alleles, which was significant for the MARS sample ($p=2\times10^{-19}$) and the combined analysis ($p=1\times10^{-16}$), but only approaching significance in the STAR*D sample (p=.084). We additionally calculated a score after weighting the number of response alleles with the respective odds ratio from the MARS sample. Using this score, we could replicate the findings with the weighted number of response alleles now reaching significance also in the STAR*D sample (OR=1.01; lower $CI_{95\%}$=1.001; p =.036).

Following a threshold model of multiple genetic influences, we additionally categorized patients as high or low response allele carriers according to their response allele score. The response allele score ranged from 253 to 361 in the MARS sample. Only one third of the MARS patients achieved remission during the first eight weeks. Considering this asymmetry, the cut-off for defining the response allele carrier status was set accordingly at 320.5 resulting in 33.3% patients of the MARS sample categorized as high response allele carriers reflecting the base rate of remission. The same threshold was applied for the STAR*D sample. The results of the survival analysis including the same set of clinical predictors are presented in Table 2b.

Consistent effects across all samples were again observed for comorbid anxiety disorder (negative effect; approaching significance in the MARS sample, p=.055) as well as for the binary score of high vs. low response alleles (positive effect; MARS: $p=1\times10^{-14}$; STAR*D: p = .036; combined analysis: 7×10^{-12}). In addition, a consistent effect was found for young age reaching significance only in the combined sample. These findings could be replicated

also for the analysis with the binary score derived from the weighted number of response alleles.

We additionally defined a binary response allele score based on the reduced set of 46 SNPs showing nominal significance in the STAR*D sample. The odds ratio for this response allele score was 2.31 ($p=5\times10^{-8}$) in MARS and 1.90 ($p=5\times10^{-9}$) in STAR*D. Comorbid anxiety disorder displayed again a negative effect (MARS: OR=.47, p=.014; STAR*D: OR=.70, p=.012). Figure 2 shows that the best outcome was observed in patients with a high number of response alleles without comorbid anxiety disorder, while the worst prognosis was obtained for patients with a low number of response alleles in combination with comorbid anxiety disorder.

Pathway analysis

As the multi-locus analysis suggested that the SNPs selected for replication in the STAR*D sample contribute additively to treatment outcome in both samples, MARS and STAR*D, we included all corresponding genes in a literature-based pathway analysis. SNPs located in intergenic regions were assigned to the nearest gene, resulting in 279 unique genes.

Pathway analysis identified 41 genes as co-cited in the same sentence with a functional descriptor in-between. These genes could be grouped into 3 clusters (Figure 3) centering on fibronectin 1 (FN1, cluster B3-1), ADAMTS-like 1 (ADAMTSL1, B3-2), and endothelin 1 (EDN1, B3-3).

FN1 from the first cluster encodes a cell surface glycoprotein mainly involved in cell adhesion processes. FN1 and five other genes of this cluster are involved in metabolic pathways. FN1 is also related with two transcription factors, MYBL2 and NR2E1, and with the substrate (EFNA5) and receptor (EPHA5) gene of ephrin-A5, an important modulator of late stage nervous system development and differentiation.

ADAMTSL1 of the second cluster encodes a protein characterized by a desintegrin and metalloproteinase with a thrombospondin motif. This cluster also includes potential risk genes for cardiovascular disorders (CD36, PON2, APOB, PIK3R1).

EDN1, center gene of the third cluster, expresses a protein involved in vasoconstriction. Further notable genes are neuregulin 1 (NRG1), a glycoprotein interacting with the NEU/ERBB2 receptor tyrosine kinase, homer homolog 1 (Drosophila) (HOMER1), a neuronal immediate early gene and modulator of glutamatergic neurotransmission, and the solute carrier family genes SLC1A2 (glutamate) and SLC6A11 (GABA).

Comment

This is the first report of a genome-wide association (GWA) analysis of antidepressant treatment response performed in patients from the Munich-Antidepressant-Response-Signature (MARS) project and in pooled DNA from an independent German replication sample. A set of 328 single nucleotide polymorphisms (SNPs) highly related to outcome in both samples was genotyped in a third sample from the Sequenced-Treatment-Alternatives-to-Relieve-Depression (STAR*D) study. Despite inclusion of more than 1,500 depressed

patients, 700 of them with genome-wide genotyping, we were unable to identify single SNP signals reaching criteria for genome wide significance suggesting that the effects of single SNPs are rather modest.

Against the backdrop of stringent statistical methods, our analysis provides experimental evidence that antidepressant drug response emerges from a multitude of genetic variants. We constructed a genotype score with the number of favorable response alleles per patient out of the set of 310 informative SNPs genotyped in all patients. This multi-locus approach revealed a significant contribution of a binary variable categorizing patients as carriers of a high vs. low number of response alleles in predicting antidepressant treatment outcome in both samples, MARS and STAR*D . This finding could be replicated after weighting the response allele score for the individual contribution of each allele. In addition, we explored the predictive effect of clinical characteristics when combined with genotype scores. We observed that patients with a comorbid anxiety disorder in combination with a low number of response alleles showed the least favorable outcome within the defined observation period. An interaction analysis showed that both effects, comorbid anxiety and the number of response alleles, were independent from each other (data not shown). In fact, this is in line with the clinical observation of a tendency for treatment resistance in the presence of comorbid anxiety disorders.[19]

A literature-based pathway analysis of functional co-citations including the genes corresponding to the SNPs of the response allele score revealed a network of 41 genes, which could be grouped into three interrelated clusters. The first cluster included the transcription factor nuclear receptor subfamily 2, group E, member 1 (NR2E1). Variations in this gene have been reported to be associated with susceptibility to bipolar disorder and schizophrenia,[36] and mice lacking this receptor display behavioral abnormalities and impaired neuronal and synaptic plasticity.[37] This cluster also includes the substrate (EFNA5) and receptor (EPHA5) genes of ephrin-A5, an important modulator of nervous system development and differentiation. This is of note, as the strongest effect with a combined phenotype of treatment outcome in the MARS sample was observed with a SNP located downstream to EPHB1, another receptor from the ephrin family. Studies with mouse mutants demonstrated that the ephrin-system regulates the neural plasticity in the hippocampus, a brain area where adult neurogenesis is stimulated by antidepressants.[38]

The second gene cluster identified in the pathway analysis includes genes related to metabolic and cardiovascular disorders frequently co-occurring with depression.[39] Potentially important findings emerged also from the third gene cluster. This cluster includes neuregulin 1 (NRG1), for which a large number of genetic studies suggested an involvement in the development of schizophrenia[40,41] and bipolar disorder,[42] and presumably also of unipolar depression.[43] Genes of this cluster are related to glutamatergic (homer homolog 1, HOMER1; glial high affinity glutamate transporter, SLC1A2) and gabaergic neurotransmission (GABA neurotransmitter transporter, SLC6A11). Mice under chronic stress treatment[44] or with increased stress susceptibility (M. Schmidt, MPI of Psychiatry, personal communication) modeling specific features of depression-like pathology displayed altered regulation of HOMER1 expression in hippocampal and cortical regions, and rats displayed altered hypothalamic HOMER1 expression after antidepressant treatment.[45] We

infer from this pathway analysis that different genetic clusters contribute to treatment outcome in depression, seemingly related to metabolic pathways and brain development (cluster 1), somatic disability (cluster 2) and to receptor signaling and neurotransmission (cluster 3).

Although we included altogether more than 1,500 patients, we were not able to replicate the pharmacogenetic effects of single SNPs. Our power analysis suggested sufficient power to detect single effects with a relative genetic risk of 1.6. It appears, however, that the effect size of single SNPs to predict antidepressant treatment response is lower than expected. This challenges the suitability of GWA for pharmacogenetic studies in complex diseases. Another limiting factor is the heterogeneity of the investigated phenotype. We tried to address this by including clinical predictors of treatment outcome, but have to concede that other factors not considered in this analysis, e.g., environmental stress or the individual drug history, most likely contributed to the heterogeneity of the phenotype. Nevertheless, we were able to replicate the additive effects of a clinical predictor and a multi-locus response-allele score. The inclusion of patients in the GWA samples suffering from bipolar depression may be regarded as confounder. However, we did not detect differences between patients with unipolar or bipolar depression with respect to the genotype frequencies of the 328 SNPs selected for replication in the STAR*D sample ($p_{corrected}>.48$; data not shown). In addition, the results of multi-locus survival analysis suggested that the diagnosis of unipolar vs. bipolar depression has no effects on treatment outcome ($p>.33$; data not shown). A further limitation is the heterogeneity of antidepressant treatments in the GWA samples. However, the primary mode of action of all antidepressants is related to an enhancement of monoaminergic neurotransmission, and despite differences in the profile of receptor occupancy antidepressants show comparable efficacy across drug classes.[46,47] Therefore, we submit that drug-specific genetic effects should be of minor importance for a genome-wide pharmacogenetic study.

Our results demonstrate the importance of multiple genetic factors in the prediction of antidepressant drug response underscoring the multifactorial nature of this trait. In particular, our findings also imply a cumulative effect of genetic variations and clinical features. Both types of variables contributed similar effects with respect to prediction of treatment outcome. Further studies will be required to confirm the suggested multi-locus approach and to investigate how the genetic variations and environmental factors converge in a set of genotypes, biomarkers and clinical features that foster the decision making process in treatment of depression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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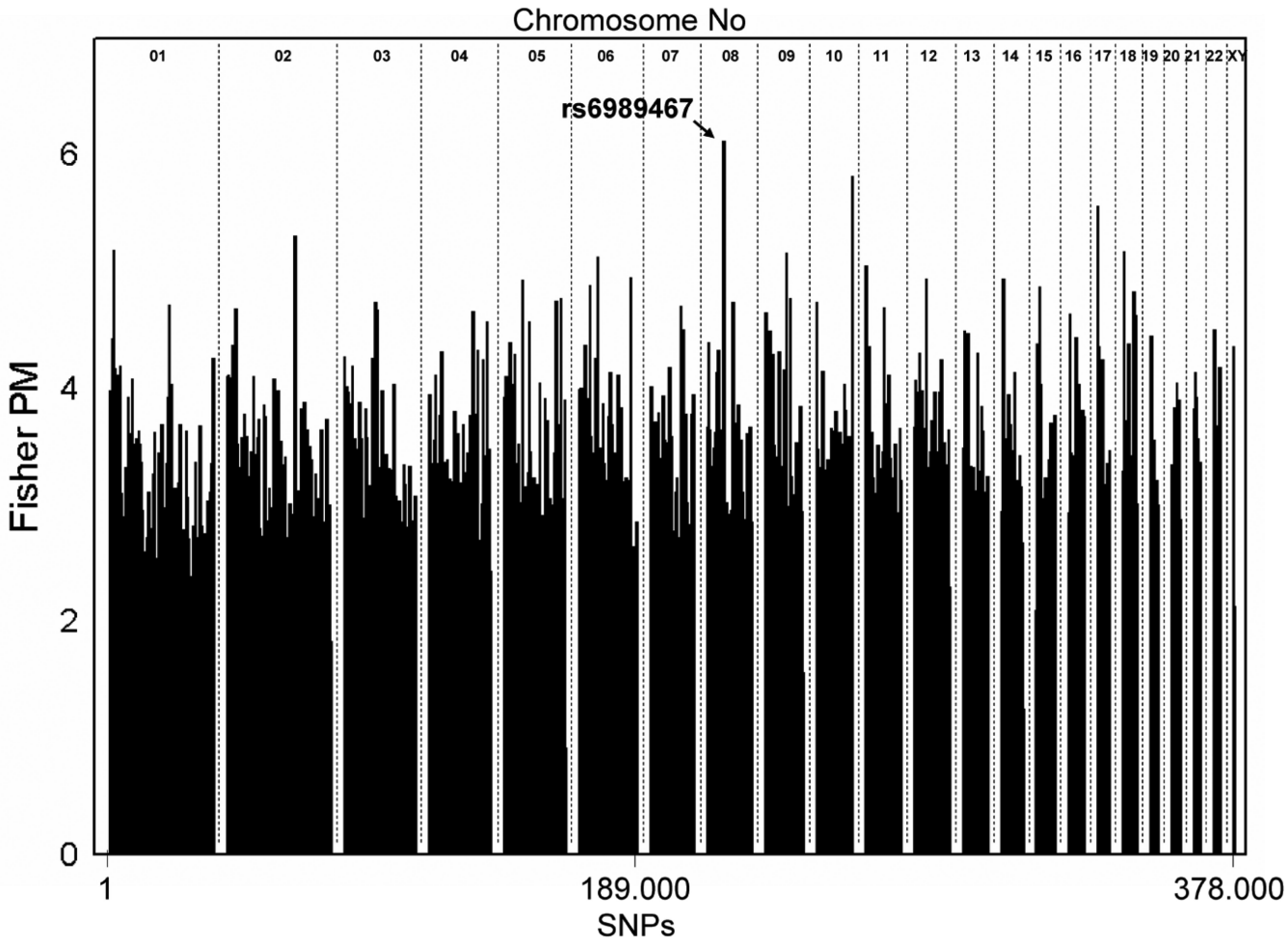

Figure 1. Genome-wide pharmacogenetic analysis of early partial response, treatment response, and remission in the MARS sample

The effect of the outcome phenotype with the highest genotypic or allelic association is presented. The highest genome-wide effect was found for rs6989467 located in the 5' flanking region to the CDH17 gene on 8q22 (displayed as negative decadic logarithm of the p value).

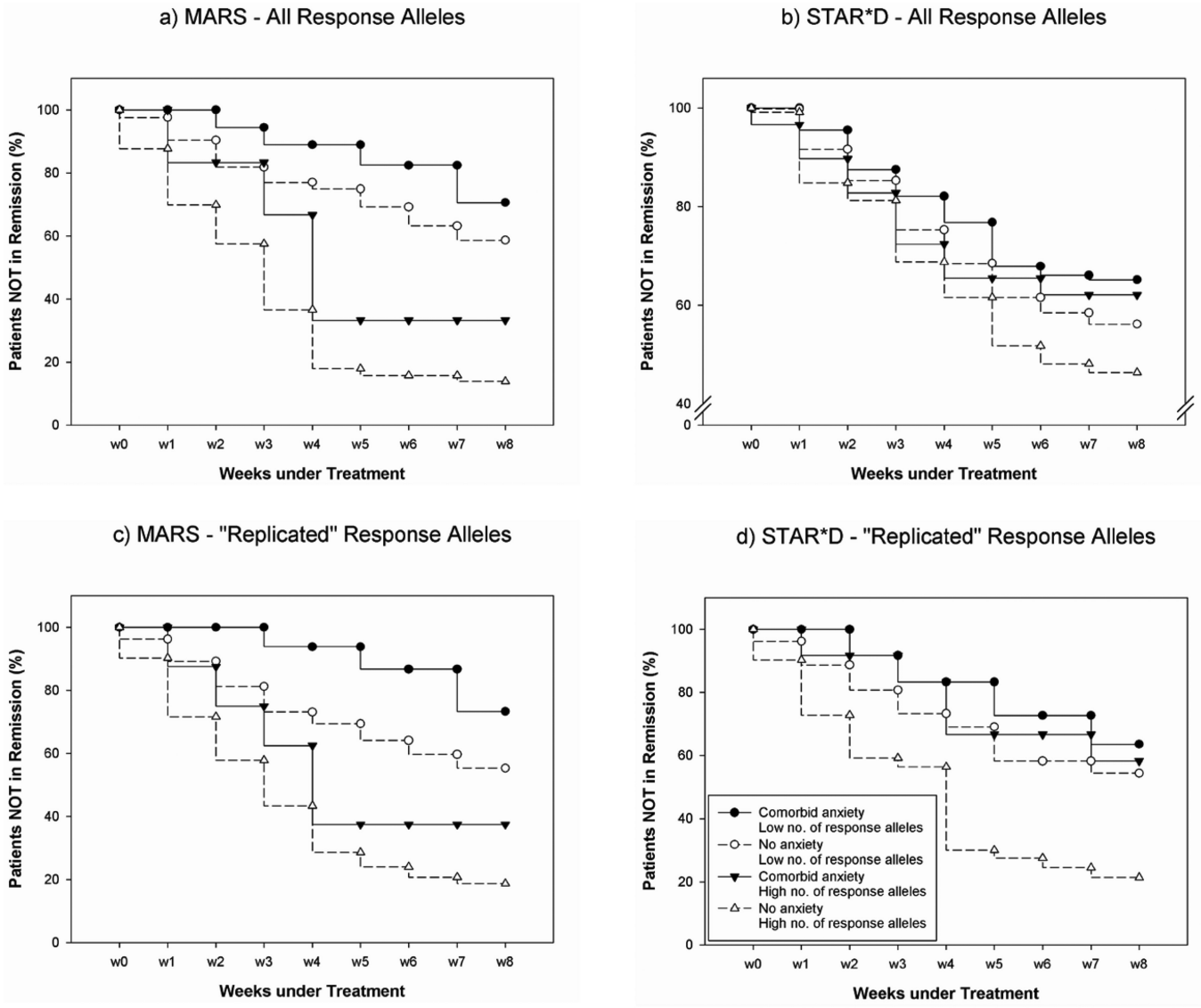

Figure 2. Effects of comorbid anxiety disorder plus high versus low number of response alleles in the MARS and STAR*D samples

Patients carrying a high number of response alleles (top 33% of the allele score distribution) without comorbid anxiety disorder (dashed line, open triangles) showed fastest remission (QIDS-C score or HAM-D equivalent of the QIDS-C score of less or equal 6) in both samples. Survival analysis revealed a large effect with an odds-ratio of 3.5 (all 310 SNPs, a) and 2.3 (46 SNPs with nominal replication, c) in the MARS sample and of 1.3 (b) and 1.9 (d), respectively, in the STAR*D sample.

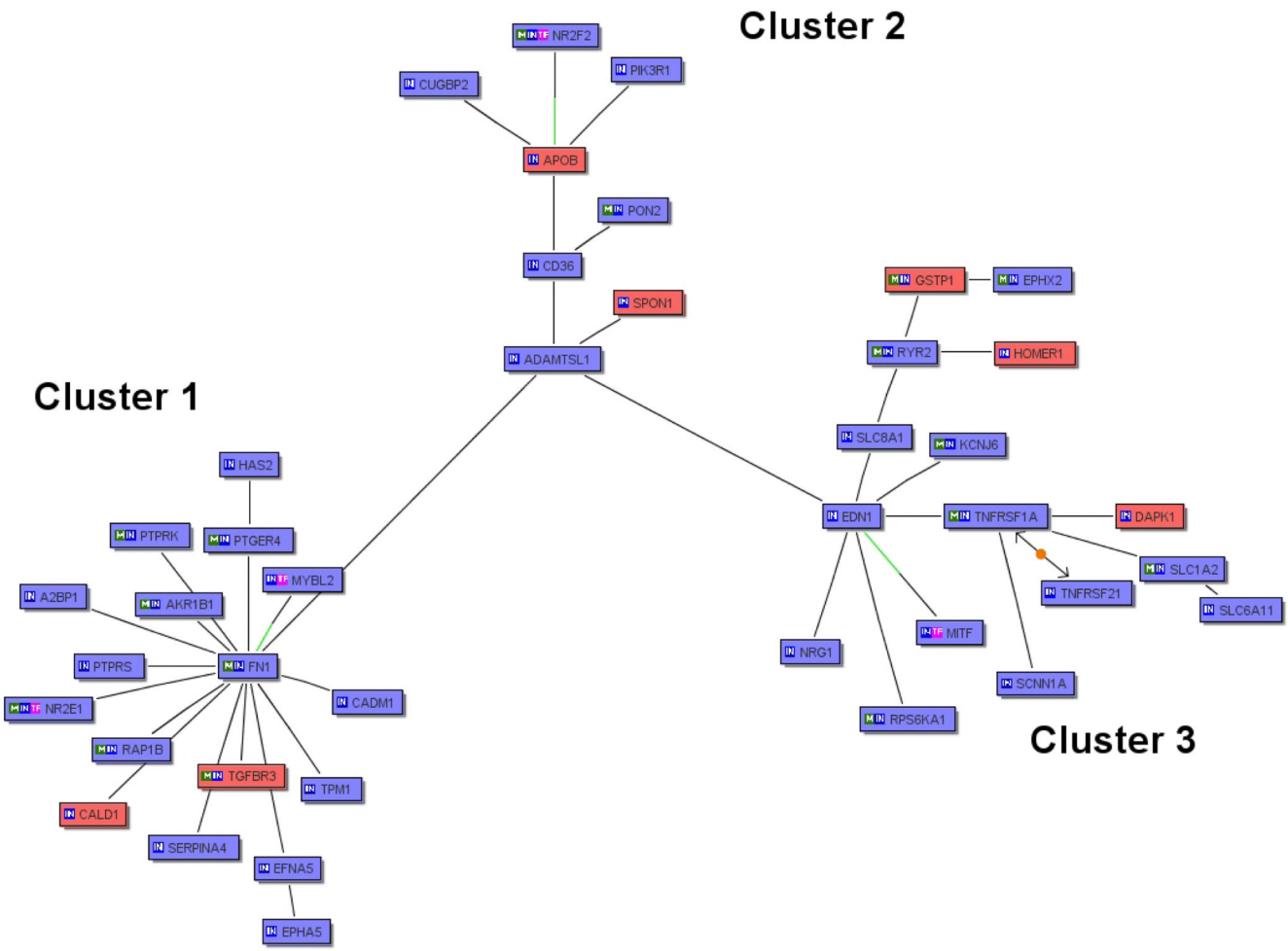

Figure 3. Results of a literature-based pathway analysis including all genes corresponding to the SNPs of the STAR*D replication

Genes were categorized as related when co-cited in the same sentence with a functional descriptor in-between. We identified 41 genes clustering around fibronectin 1 (FN1) (Cluster 1), ADAMTS-like 1 (ADAMTSL1) (Cluster 2), and endothelin 1 (EDN1) (Cluster 3).

Note. Genes with corresponding SNPs achieving a nominal significant replication in the STAR*D sample shaded in red; green line indicates transcription factor binding site match in target promoter; line with yellow mark indicates annotation by Molecular Connections experts. IN := input gene; TF: = transcription factor; M := part of a metabolic pathway.

Table 1

Demographic and clinical sample characteristics

	MARS	German Replication Sample	STAR*D	p[1]
N (% women)	339 (56.0%)	361 (60.7%)	832 (57.9%)	.456
Age (± SD)	49.0 ± 14.5	48.8 ± 14.4	42.9 ± 13.5	< .001
Caucasian	100%	100%	100%	1.00
Depression Diagnoses				
Single Episode (%)	90 (26.5%)	92 (25.5%)	178 (21.4%)	< .001
Recurrent Depression	211 (62.2%)	213 (59.1%)	654 (78.6%)	
Bipolar Disorder	38 (11.3%)	56 (15.4%)	0 (0.0%)	
Comorbid Anxiety	24 (7.1%)	104 (28.9%)	155 (18.6%)	< .001
Illness-related variables				
Age at onset	37.5 ± 15.7	37.1 ± 13.6	25.8 ± 14.6	< .001
Duration of current Episode (weeks)	40.5 ± 73.1	N.A.	94.6 ± 218	< .001
QIDS at inclusion[2]	18.4 ± 4.2	17.0 ± 4.6	15.9 ± 3.1	< .001

[1] P values (two-tailed) of Pearson Chi[2] tests (qualitative data) and univariate analysis of variance (quantitative data) are reported.

[2] HAM-D values from the MARS and the German Replication samples were translated into QIDS scores according to the conversion table suggested by Rush et al.[23]

Table 2a

Cox Regression results predicting remission (QIDS-C ≤ 6) during the first eight weeks of antidepressant treatment including clinical characteristics and the number of response allele score as predictors.

	Model		Gender[1]		Age		Age at onset		Recurrent episode[2]		Chronic episode[2]		Comorbid anxiety[2]		"Response" allele score	
	Chi^2_7	**p**	**OR [CI_{95}]**	**p**	**OR [CL_{95}]**	**p**	**OR [CL_{95}]**	**p**	**OR [CI_{95}]**	**p**	**OR [CL_{95}]**	**p**	**OR [CL_{95}]**	**p**	**OR [CL_{95}]**	**p**
MARS	*99.09*	*2×10^{-18}*	0.88 [1.14]	ns	0.99 [1.01]	ns	0.99 [1.01]	ns	1.17 [0.85]	ns	0.79 [1.32]	ns	*0.50 [0.89]*	*0.024*	*1.04 [1.03]*	*2×10^{-19}*
STAR*D	*14.64*	*.041*	*1.22 [1.01]*	*0.045*	0.99 [1.01]	ns	0.99 [1.01]	ns	0.96 [1.27]	ns	1.14 [0.91]	ns	*0.67 [0.87]*	*0.006*	*1.01 [1.00]*	*0.084*
Combined	*83.84*	*2×10^{-15}*	1.06 [0.91]	ns	*0.99 [0.99]*	*0.047*	1.01 [0.99]	ns	1.04 [0.84]	ns	1.04 [0.85]	ns	*0.61 [0.78]*	*3×10^{-4}*	*1.02 [1.02]*	*1×10^{-16}*

Note. One-sided 95% confidence interval limits (CI_{95}) of the Odds ratio (OR) and one-sided p-values in favor of the prediction hypothesis are reported. Significant effects are in boldface type.

[1] Gender coded as "1" for male and "2" for female patients

[2] Recurrent or chronic episode (duration of current episode ≥ 2 years) and comorbid anxiety (general anxiety disorder, panic disorder, social phobia) coded as "1" for true and "0" for false. One-sided p-values in favor of the prediction hypothesis are reported.

Table 2b

Cox Regression results predicting remission (QIDS-C ≤ 6) during the first eight weeks of antidepressant treatment including clinical characteristics and the binary score of high vs. low number of response alleles as predictors.

	Model		Gender[1]		Age		Age at onset		Recurrent episode[2]		Chronic episode[2]		Comorbid anxiety[2]		High/low "response" alleles[3]	
	Chi^2_7	**p**	**OR [CI_{95}]**	**p**	**OR [CL_{95}]**	**p**	**OR [CL_{95}]**	**p**	**OR [CI_{95}]**	**p**	**OR [CL_{95}]**	**p**	**OR [CL_{95}]**	**p**	**OR [CL_{95}]**	**p**
MARS	*77.24*	*5×10^{-14}*	0.90 [1.16]	ns	*0.99 [1.01]*	*0.050*	1.01 [0.99]	ns	1.22 [0.89]	ns	0.82 [1.36]	ns	*0.58 [1.02]*	*0.055*	*3.52 [2.69]*	*1×10^{-14}*
STAR*D	*15.97*	*.025*	*1.21 [1.00]*	*0.052*	*0.99 [1.00]*	*0.091*	0.99 [1.01]	ns	0.95 [1.27]	ns	1.13 [0.90]	ns	*0.68 [0.88]*	*0.006*	*1.28 [1.02]*	*0.036*
Combined	*63.16*	*4×10^{-11}*	1.06 [0.91]	ns	*0.99 [0.99]*	*0.015*	1.01 [0.99]	ns	1.04 [0.84]	ns	1.03 [0.85]	ns	*0.64 [0.81]*	*8×10^{-4}*	*1.96 [1.67]*	*7×10^{-12}*

Note. One-sided 95% confidence interval limits (CI_{95}) of the Odds ratio (OR) and one-sided p-values in favor of the prediction hypothesis are reported. Significant effects are in boldface type.

[1] Gender coded as "1" for male and "2" for female patients

[2] Recurrent (at least one previous depressive episode) or chronic depression (duration of current episode ≥ 2 years) and comorbid anxiety (general anxiety disorder, panic disorder, social phobia) coded as "1" for true and "0" for false

[3] Cut-off for high versus low number of "response alleles" was set at 66.7% of the quantitative allele score distribution corresponding to the expected number of remitters after eight weeks (33.3%) according to MARS data.