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The *FKBP5*-gene in depression and treatment response – an association study in the STAR*D-cohort

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Abstract

Background—In a recent study of several antidepressants in hospitalized, non-Hispanic White patients, Binder et al. reported association of markers located within the *FKBP5* gene with treatment response after 2 and 5 weeks. Individuals homozygous for the TT-genotype at one of the markers (rs1360780) reported more depressive episodes and responded better to antidepressant treatment. There was no association between markers in *FKBP5* and disease. The present study aimed at

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studying the associated *FKBP5* markers in the ethnically diverse STAR*D sample of non-hospitalized patients treated with citalopram.

Methods—We used clinical data and DNA samples from 1809 outpatients with non-psychotic major depressive disorder (DSM-IV criteria), who received up to 14 weeks of citalopram. A subset of 1523 patients of White non-Hispanic or Black race was matched with 739 controls for a case-control analysis. The markers rs1360780 and rs4713916 were genotyped on the Illumina platform. TaqMan-assay was used for marker rs3800373.

Results—In the case-control analysis, marker rs1360780 was significantly associated with disease status in the White non-Hispanic sample after correction for multiple testing. A significant association was also found between rs4713916 and remission. Markers rs1360780 and rs4713916 were in strong LD in the White non-Hispanic but not in the Black population. There was no significant difference in the number of previous episodes of depression between genotypes at any of the three markers.

Conclusion—These results indicate that *FKBP5* is an important target for further studies of depression and treatment response.

Introduction

Major depressive disorder (MDD) is a debilitating disease with a high prevalence (16.2% according to the most recent National Comorbidity Survey (1)). In the year 2020, depressive disorders are estimated to be one of the top ranked disease burdens world wide (2,3). Finding more effective interventions for depression must therefore have high priority for clinical and basic research efforts.

With pharmacological treatment options available today, only a minority of the patients disabled by depression experience full remission (4–6). In addition, clinical and pharmacogenetic studies have shown strong individual variation in treatment outcome and side effects with antidepressants (7–10).

Different methods are used to elucidate possible genetic determinants of susceptibility for depression as well as prediction of success when treating the disease. While whole-genome assays will shortly become available, up to now most studies have employed candidate-gene approaches based on known gene function in mood and depression.

Candidate genes regularly include members of the main neurotransmitter systems such as serotonin, dopamine and glutamate (11–13). However, other pathways that have influence over several neuroendocrine systems have recently received considerable attention. One such pathway, the Hypothalamic-Pituitary-Adrenal axis (HPA-axis), plays a major role in stress hormone regulation (14,15).

A study by Binder and collaborators (16) has suggested that single-nucleotide polymorphisms (SNPs) in the *FKBP5*-gene are associated with outcome of antidepressant treatment and recurrence in major depression. The *FKBP5*-gene codes for a chaperone protein important for fine-tuning of the HPA-axis. In further analyses, it was shown that the TT-homozygote genotype of the marker rs1360780 was most strongly associated with better treatment response and more previous depressive episodes. No association of *FKBP5* markers with disease status was observed.

While the Binder et al. study provided a very interesting new lead on involvement of *FKBP5* in treatment response, the study had several limitations. The sample size was relatively modest for detecting risk loci of small effect, the study only included hospitalized patients and contained both psychotic and non-psychotic depression, and the sample was limited to individuals of White non-Hispanic ancestry.

The objective of the present study was to investigate correlation of the associated markers with treatment-response in an ethnically diverse sample of non-hospitalized, non-psychotic depressed patients using data generated within the STAR*D study, the largest treatment-response study carried out to date.

The genetic sub-study of STAR*D was carried out following a pre-agreed analysis plan employing a two-split design in order to correct for multiple testing. Findings of significant associations have been summarized in two reports (9,10) that did not include the *FKBP5*-gene among the reported associations. However, the split sample design we employed may have reduced power to detect a genuine association with *FKBP5*.

In order to maximize power to detect such association, this report therefore did not employ a two-split design. Rather, data from all 1809 treated individuals with available genotypes were analyzed together herein. Correction for multiple testing was carried out using the Bonferroni method. Similarly to the Binder et al. study, we also tested whether *FKBP5* markers might show association with the diagnosis of depression itself and the number of depressive episodes.

Methods and Materials

Patients and study design

This study presents data obtained from level 1 of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, whose overall study design has been described elsewhere (17–19). Diagnoses were established according to DSM-IV criteria, and only non-psychotic major depressive disorder was included. A diagnosis of bipolar disorder led to exclusion from the study.

The treatment regime at level 1 aimed to evaluate outcome of treatment with the antidepressant drug citalopram (18,20). To reduce the risk of inadequate dosing, and to ensure that patients who progressed to the next level of treatment were truly resistant to the level 1 treatment, the study was carried out with a desired end point after 14 weeks of treatment which is regarded as a long enough period for adjusting an optimal dosage and evaluating the corresponding effects. If deemed necessary, patients were, however, allowed to proceed into level 2 before 14 weeks of treatment, and were included in this analysis if they had received at least 6 weeks of treatment with citalopram. Participating individuals were recruited without regard to race or ethnicity. Self-reported race and ethnicity data were used for group assignment. For this report, race was collapsed into 'White', 'Black' or 'other'; the White sample was further divided into 'Hispanic' or 'Non-Hispanic' (10). The group of individuals reporting 'other' ethnic origin was too small and inhomogeneous to be analyzed separately. Thus, these individuals only appear in the 'total' sample. The STRUCTURE software package (21–23) was used to assess possible population structure as described previously (9). No evidence for population structure was seen in the sample self-described as 'White, non-Hispanic'.

The total number of available individuals at each visit is presented in supplementary figure 1. The numbers were reduced from each time point to the next by those who went to follow-up with a satisfactory outcome, as well as those who dropped out of the study or moved on to level 2 treatment. Note also that not all individuals attended each planned study visit. Those patients, for example, that failed to attend the visit after 2 weeks were still included in the calculations of QIDS-C₁₆ score means for the following study visits. For the case-control analysis, DNA samples were used only from the White non-Hispanic-and Black sub-populations (see CONSORT diagram, supplementary figure 2).

Controls

Control DNAs (N=739) were provided by the Rutgers Cell Repository, and originated from the collection of normal individuals collected under auspices of the NIMH genetic initiative (see supplementary figure 2b). All control samples were screened (DSM-IV) for major depression, bipolar disorder and psychosis, by self report, and affected individuals were excluded (10).

DNA samples and genotyping

After written informed consent and approval of the study protocol by Medical Centers, Data Coordinating Centers, and the Data Safety and Monitoring Board of NIMH (17,24), blood samples were drawn from 1953 participants of the total of 4041 participants in the STAR*D study. 95 individuals had to be excluded from the study due to missing clinical data, insufficient baseline depression (QIDS-C₁₆ < 10), non-compliance with treatment protocol, or suspected sample mix-ups (see supplementary figure 2a). Of the remaining 1858 samples, 15 were excluded due to late baseline score (baseline QIDS-C₁₆ score later than within 2 weeks of treatment), genotypes were not available from 34 individuals, and a total of 1809 eligible and successfully genotyped DNAs were included in the analyses presented herein.

Genotypes for the two *FKBP5*-markers rs1360780 and rs4713916 were determined at Illumina (San Diego, USA) using a standard protocol with a success of 99.78%. TaqMan assay was used in-house (F.J.M. lab) for determination of genotypes at the marker rs3800373.

Measurements of change of depression severity

The clinician-rated 16-item Quick Inventory of Depressive Symptomatology (QIDS-C₁₆) (25–28) was used to measure treatment response at each treatment visit and at the end of the treatment period of up to 14 weeks.

In the categorized outcome definition (9), remitters were defined as having a QIDS-C₁₆ score ≤5 at endpoint of the level 1 treatment, whereas non-remitters still had a QIDS-C₁₆ score ≥10 at the last visit, as long as they were not classified as intolerant of the medication. In a parallel analysis, response was defined as a 50% reduction of QIDS-C₁₆ score at the last treatment visit and non-response as less than a 40% reduction. Individuals that received scores in between these ranges or had less than 6 weeks of treatment were excluded from the respective analyses in order to minimize the risk for misclassification. After such exclusions, a total of 1370 individuals were eligible for the treatment-response study when response was the outcome, and 1190 individuals were eligible when the outcome was remission.

The quantitative analyses presented herein used the raw QIDS-C₁₆ scores at each visit. Analysis of the number of previous depressive episodes was carried out based on self-reported estimates.

Statistical analysis

In the case-control and treatment-response studies, tests for significance were calculated in UNPHASED 3.0.5 (<http://www.mrc-bsu.cam.ac.uk/personal/frank/software/unphased/>) and Haploview 3.2 (<http://www.broad.mit.edu/mpg/haploview/>), which gave virtually identical results for the allele-wise tests. UNPHASED was also used for genotype-based analyses. Determination of statistical significance was made by a two-sided likelihood-ratio test at an alpha-level of 5%. Hardy-Weinberg Equilibrium (HWE) was tested for by a chi-squared goodness-of-fit test. Correction for multiple testing was carried out with a factor of 12 in the case-control study (3 markers * 2 populations * 2 tests, allele- and genotype-wise) and a factor of 18 in the treatment-response study (3 markers * 3 populations * 2 tests, allele- and genotype-wise).

For the analysis of QIDS-C₁₆ scores at different time points during the study, a quantitative association test was performed by one-way ANOVA. In addition, a Tukey-Kramer test (alpha-level of 5%) was used as *post-hoc* analysis and correction for multiple testing was carried out using the Bonferroni method (due to substantially different composition of the sample at the different time points).

Association with number of episodes of depression in the past was calculated using one-way ANOVA. As a *post hoc* test, Tukey-Kramer procedure was applied with an alpha level of 5%. Because three markers were tested in three groups, Bonferroni correction was carried out with a factor of 9.

Results

Case-control study

In the comparison of cases and controls, nominally significant associations of markers rs1360780 and rs4713916 with disease were identified in the White non-Hispanic population in a genotype-wise test (table 1a). However, only the finding in rs1360780 remained significant after correction for multiple testing ($p = 0.046$). The CC-genotype was more frequent in controls than in cases (50% vs. 44%), while the TC-heterozygote genotype was over-represented in cases (46% vs. 38%). No significant association was seen in Blacks. No significant association was seen in an allele-wise test (table 1b). Both markers were found to be in Hardy Weinberg Equilibrium in cases and controls within each population (data not shown).

Treatment-response analysis

A genotype based association test with treatment-response showed significant association of rs4713916 with remission but not with response when all racial groups were analyzed together (table 2a–b). Dividing the sample into the different racial groups revealed that the association was mainly driven by an association within the white non-Hispanic population.

In addition to the genotype-wise test chosen by Binder et al., we also tested an additive disease model by carrying out an allele-wise association test (table 3a–b). Results from this test were very similar to the genotype-wise tests. The A-allele of rs4713916 was significantly over-represented in remitters in the combined sample (table 3a).

Odds ratio comparisons

Table 3a–b shows odds ratios, allele frequencies and results from the allele-wise association tests. The direction of association was reversed for markers rs1360780 and rs3800373 in the Black population. This led us to carry out a test for determining the degree of linkage disequilibrium (LD) between the markers in the White non-Hispanic and the Black subpopulations. In the White non-Hispanic population the markers rs1360780 and rs4713916 were in strong LD (r^2 of 0.67). Marker rs4713916 and rs3800373 were also in strong LD (r^2 of 0.54). In the Black population these markers were in much weaker LD: the r^2 was only of 0.09 between rs1360780 and rs4713916, and 0.08 between rs4713916 and rs3800373. Markers rs1360780 and rs3800373 were in strong LD both in the White non-Hispanics and Blacks ($r^2 = 0.86$ in both populations). This suggests that in White non-Hispanics, all three markers reside in one haplotype block, as suggested by Binder et al., while in Blacks there are at least two different blocks in this genomic interval, where rs1360780 and rs3800373 belong to one block and rs4713916 belongs to a different block.

Quantitative analysis over 14 weeks

Binder et al. presented a difference in depression scores between genotypes over the treatment period. Our study has several limitations that do not allow us to directly aim to replicate that finding (see discussion for further details). We here only present genotype-wise QIDS-C₁₆ scores over time in the White non-Hispanic population, which was the largest sub-sample in our study (Figure 1 a–c). For each genotype, mean QIDS-C₁₆ scores were plotted against time during the 14 weeks of treatment for markers rs1360780, rs4713916 and rs3800373.

Carriers of all genotypes responded to the treatment with citalopram with a similar slope of the curve as observed by Binder et al. A nominally significant difference between genotype groups was only seen in homozygote carriers of the C-allele in the marker rs3800373 after 4 weeks of treatment ($p = 0.02$ by ANOVA). This p -value, however, did not hold up for correction for multiple testing (see methods).

Prior episodes of depression

In an analysis of prior episodes of depression, none of the observed differences (figure 2a–c) between genotypes in the markers rs1360780, rs4713916 or rs3800373 was of sufficient magnitude to reach significance when analyzed with one-way ANOVA.

Discussion

Case-control study

Sufficient power to detect association of genotype to phenotype can only be obtained with large sample sizes (29), especially when genes that only partially contribute to the disease susceptibility shall be identified. Furthermore, association signals must be strong enough to survive correction for multiple testing, as carried out in this study as well as in the original *FKBP5*-study.

The present case-control analysis was carried out including 1256 White non-Hispanic individuals matched with 634 controls, as well as 267 Black individuals matched with 105 controls.

Our analyses showed significant association (corrected p -value = 0.046) of the marker rs1360780 with disease status. This association was only seen in White non-Hispanics. In contrast to our results, the Binder et al. study did not reveal significant association after correction for multiple testing, when 294 hospitalized individuals were studied together with 339 matched controls. Failure to detect such association in the original study may be due to insufficient power due to a relatively small sample size, as well as the need for correction for a large number of independent tests.

Treatment-response analysis

Given the prior finding by Binder et al., we herein did not correct for all markers that were included in the original STAR*D study of treatment response, but only for those tests that specifically aimed at replicating the analysis plan employed by Binder et al., focusing on three previously associated markers in the *FKBP5*-gene.

Association tests for evaluation of treatment outcome showed nominally significant association of marker rs4713916 with both remission and response when all racial/ethnic populations were studied together. However, only the association with remission survived correction for multiple testing (table 2a–b, 3a–b).

Tests of LD of the three markers in *FKBP5* revealed the presence of at least two different haplotype blocks in this genomic interval in the Black population, compared to the single block of strong LD observed in the Whites. Inclusion of Blacks in our study may thus provide an indication towards the functional allele causing the observed associations, since in the Black sample, rs4713916 and rs1360780 segregate almost independently.

Based on the observed LD patterns, our study points to the promoter-SNP rs4713916 as the putative functional region rather than the intronic rs1360780 or rs3800373, located in the 3'-prime untranslated region (3'-UTR).

Quantitative analysis over 14 weeks

The STAR*D study design has some severe limitations regarding analyses at different time points since data from individual outcome in treatment response is not available from all weeks during the period of up to 14 weeks of treatment. Enrolled individuals may end earlier than the defined end point due to remission, side effects, or drop outs. In addition, all individuals did not attend each clinic visit at 2, 4, 6, 9, 12 and 14 weeks. Our results did not show any significant differences between genotypes in either the total sample or in the sub-samples. The fact that no significant association was seen in our analysis may, however, simply be due to the above-described limitations of our study design regarding such calculations.

Number of previous episodes

The number of prior episodes of depression was assessed in relation to the different genotypes.

Our results did not show any differences between genotypes and number of lifetime depressive episodes in any of the three markers. This is contrary to the results of Binder et al., who observed more depressive episodes in this group.

This discrepancy between the studies can, however, be due to the methods used to ascertain the actual number of episodes, which is often difficult as it relies on patients' recall abilities and different definitions as to when an episode has truly ended.

General remarks

Clinical trials designed to determine the efficacy of antidepressant agents need to be able to differentiate between placebo and true pharmacological effects (30). This, however, is difficult to realize in the pharmacogenetic setting. The genetic analysis is performed at the level of the individual rather than the group, and it is impossible to predict how an individual with a certain genotype would have responded if they had been given a placebo only. Therefore, pharmacogenetic studies such as the present study and the Binder et al. study have limitations. None of the studies has included a positive or a negative control for the antidepressant treatment, and thus could not distinguish pharmacological response from placebo response to assess the absolute effect as well as the relative effect.

Our study provides further evidence for an association of *FKBP5*-markers with treatment response to antidepressant treatment when using the categorical 'responder' and 'remitter' outcomes, which were the primary outcomes in the STAR*D study design. Our definitions of remission and response were designed to allow for sufficiently long treatment with citalopram, aiming at eliminating as much of a confounding placebo response as possible in the primary outcomes. Association of a marker in *FKBP5* with depression and remission after citalopram treatment provides further evidence that dysregulation of the HPA axis in depression is not only an epiphenomenon of the disease (31). Rather, knowledge about individual variation in components of HPA-axis regulation may lead to prediction of clinical phenotypes and outcome of antidepressant treatment.

To summarize, the results provide further modest evidence for association of *FKBP5* markers with treatment response to the SSRI citalopram and evidence for an association with depression itself. Odds ratios identified in the present report for the treatment response phenotype are considerably lower than those reported by Binder et al., which may be due to the fact that our study used outpatients who may have had a higher likelihood of response to the nonspecific (“placebo”) effects of treatment as compared to hospitalized individuals. Another possible explanation could be the “winners curse” phenomenon, according to which the first study identifying an effect tends to over-estimate effect sizes.

We conclude that *FKBP5* remains an interesting gene target both for depression and treatment response to SSRIs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. QIDS-C₁₆ scores by genotype over time measured in the White non-Hispanic population. After correction for multiple testing no significant difference in outcome of treatment response were seen when analyzed with one-way ANOVA. **A**; marker rs1360780. **B**; marker rs4713916. **C**; marker rs3800373.

Figure 2.

Number of previous episodes of depression in the past, genotype-wise. No significant difference in the number of episodes of depression between genotypes was seen in any of the markers. Between markers where columns differ in size, mean and S.E.M. values are presented. **A:** All ethnic groups (n=1534). Mean and S.E.M values for TT- and TC-genotypes in the marker rs1360780; 4.28, 0.38 and 4.98, 0.20. Mean and S.E.M.. values for AA- and AG-genotypes at the marker rs4713916; 3.91, 0.43 and 5.0, 0.21. **B:** White non-Hispanic population (n=1117). Mean and S.E.M values for TT- and TC-genotypes in the marker rs1360780; 4.04, 0.43 and 4.75, 0.23. Mean and S.E.M. values for AA- and AG-genotypes in the marker rs4713916; 3.70, 0.49 and 4.69, 0.23. **C:** Black population (n=189). Mean and S.E.M values

for TT- and TC-genotypes in the marker rs1360780; 5.19, 1.27 and 6.12, 0.61. Mean and S.E.M. values for AA- and AG-genotypes in the marker rs4713916; 3.68, 1.02 and 6.25 and 0.72. Mean and S.E.M. values for AA- and AC-genotypes in the marker rs3800370; 5.14, 0.65 and 6.33, 0.68.

Table 1

Case-control study in the White non-Hispanic and Black samples for all three markers in the FKBP-gene. Odds-ratio values (OR) as well as the upper (Hi) and lower (Lo) values from the 95% confidence interval (C.I.) are presented. Overall p-values from association tests are shown, both as nominal values and after correction for multiple testing (correction factor of 12) (n.s = not significant).

Table 1a											
Ethnic group	SNP	Cases		Controls		OR (C.I., Lo-Hi)		Nominal p-value		Corrected p-value	
White n-H	rs1360780	TT, 125 (0.10)	TC, 581 (0.46)	TT, 72 (0.11)	TC, 243 (0.38)	CC, 319 (0.50)	TT/TC, 0.72 (0.51-1.01)	TC/CC, 1.39 (1.14-1.70)	0.0038	0.046	0.046
	rs4713916	AA, 115 (0.092)	AG, 557 (0.44)	AA, 60 (0.095)	AG, 244 (0.39)	GG, 330 (0.52)	AA/AG, 0.84 (0.59-1.19)	AG/GG, 1.29 (1.05-1.58)	0.046	n.s	n.s
	rs3800373	AA, 590 (0.48)	AC, 531 (0.43)	AA, 308 (0.52)	AC, 228 (0.39)	CC, 55 (0.09)	AA/AC, 0.82 (0.67-1.01)	AC/CC, 1.16 (0.80-1.66)	0.18	n.s	n.s
Black	rs1360780	TT, 45 (0.17)	TC, 131 (0.49)	TT, 17 (0.16)	TC, 47 (0.45)	CC, 41 (0.39)	TT/TC, 0.95 (0.49-1.82)	TC/CC, 1.19 (0.62-2.29)	0.66	n.s	n.s
	rs4713916	AA, 1 (0.004)	AG, 49 (0.18)	AA, 1 (0.01)	AG, 20 (0.19)	GG, 84 (0.80)	AA/AG, 0.37 (0.02-7.88)	AG/GG, 0.95 (0.53-1.70)	0.8	n.s	n.s
	rs3800373	AA, 83 (0.31)	AC, 135 (0.51)	AA, 41 (0.41)	AC, 44 (0.44)	CC, 15 (0.15)	AA/AC, 0.66 (0.40-1.09)	AC/CC, 1.0 (0.51-1.96)	0.23	n.s	n.s
Table 1b											
Ethnic group	SNP	Cases		Controls		OR (C.I., Lo-Hi)		Nominal p-value		Corrected p-value	
White n-H	rs1360780	T, 831 (0.33)	C, 1675 (0.67)	T, 387 (0.31)	C, 881 (0.69)	T/C, 1.13 (0.98-1.30)		0.1		n.s	
	rs4713916	A, 787 (0.31)	G, 1725 (0.69)	A, 364 (0.29)	G, 904 (0.71)	A/G, 1.13 (0.98-1.31)		0.097		n.s	
	rs3800373	A, 1711 (0.69)	C, 753 (0.31)	A, 844 (0.71)	C, 338 (0.29)	A/C, 0.91 (0.78-1.06)		0.22		n.s	
Black	rs1360780	T, 221 (0.41)	C, 313 (0.59)	T, 81 (0.39)	C, 129 (0.61)	T/C, 1.12 (0.82-1.55)		0.49		n.s	
	rs4713916	A, 51 (0.096)	G, 483 (0.905)	A, 22 (0.10)	G, 188 (0.90)	A/G, 0.9 (0.53-1.54)		0.7		n.s	
	rs3800373	A, 301 (0.57)	C, 227 (0.43)	A, 126 (0.63)	C, 74 (0.37)	A/C, 0.78 (0.56-1.09)		0.14		n.s	

* frequencies in parentheses. **a)** Genotype-wise test. **b)** Allele-wise test.

Table 2

Results from genotypic association tests for outcome in treatment-response in the total sample (all ethnicities) as well as sub-samples (White non-Hispanic and Black). The table also presents odds-ratio values (OR) as well as the upper (Hi) and lower (Lo) values from the 95% confidence interval (C.I.). Overall p-values from association tests are shown, both as nominal values and after correction for multiple testing (correction factor of 18) (n.s = not significant).

Table 2a													
Ethnic group	SNP	Remitter			Non-remitter			OR (C.I., Lo-Hi)			Nominal p-value	Corrected p-value	
All	rs1360780	TT, 81 (0.11)	TC, 334 (0.46)	CC, 307 (0.43)	TT, 54 (0.12)	TC, 199 (0.43)	CC, 213 (0.46)	TT/TC, 0.89 (0.61-1.32)	TT/CC, 1.04 (0.71-1.53)	TC/CC, 1.16 (0.91-1.49)	0.47	n.s	n.s
	rs4713916	AA, 69 (0.10)	AG, 295 (0.41)	GG, 359 (0.50)	AA, 33 (0.07)	AG, 155 (0.33)	GG, 279 (0.60)	AA/AG, 1.10 (0.70-1.73)	AA/GG, 1.60 (1.04-2.43)	AG/GG, 1.47 (1.15-1.88)	0.002708	0.049	
	rs3800373	AA, 324 (0.46)	AC, 311 (0.44)	CC, 76 (0.11)	AA, 220 (0.48)	AC, 189 (0.41)	CC, 50 (0.11)	AA/AC, 0.90 (0.70-1.15)	AA/CC, 0.97 (0.65-1.44)	AC/CC, 1.08 (0.72-1.62)	0.68	n.s	
White n-H	rs1360780	TT, 52 (0.10)	TC, 249 (0.48)	CC, 215 (0.42)	TT, 30 (0.11)	TC, 110 (0.39)	CC, 143 (0.51)	TT/TC, 0.76 (0.45-1.27)	TT/CC, 1.15 (0.70-1.88)	TC/CC, 1.50 (1.11-2.04)	0.032	n.s	
	rs4713916	AA, 56 (0.11)	AG, 242 (0.47)	GG, 219 (0.42)	AA, 25 (0.09)	AG, 107 (0.38)	GG, 152 (0.54)	AA/AG, 0.99 (0.59-1.67)	AA/GG, 1.53 (0.93-2.50)	AG/GG, 1.56 (1.15-2.12)	0.01	n.s	
	rs3800373	AA, 234 (0.46)	AC, 225 (0.44)	CC, 48 (0.09)	AA, 149 (0.53)	AC, 106 (0.38)	CC, 25 (0.09)	AA/AC, 0.74 (0.55-1.01)	AA/CC, 0.82 (0.49-1.37)	AC/CC, 1.11 (0.64-1.90)	0.15	n.s	
Black	rs1360780	TT, 14 (0.16)	TC, 42 (0.48)	CC, 31 (0.36)	TT, 13 (0.16)	TC, 48 (0.58)	CC, 22 (0.27)	TT/TC, 1.23 (0.52-2.90)	TT/CC, 0.77 (0.30-1.94)	TC/CC, 0.63 (0.32-1.23)	0.39	n.s	
	rs4713916	AA, 0 (0.0)	AG, 15 (0.174)	GG, 71 (0.826)	AA, 0 (0.0)	AG, 14 (0.169)	GG, 69 (0.831)	n.a.	n.a.	AG/GG, 1.04 (0.47-2.31)	0.92	n.s	
	rs3800373	AA, 27 (0.31)	AC, 47 (0.54)	CC, 13 (0.15)	AA, 22 (0.27)	AC, 44 (0.54)	CC, 16 (0.20)	AA/AC, 1.15 (0.57-2.30)	AA/CC, 1.50 (0.60-3.74)	AC/CC, 1.31 (0.57-3.01)	0.68	n.s	
Table 2b													
Ethnic group	SNP	Responder			Non-responder			OR (C.I., Lo - Hi)			Nominal p-value	Corrected p-value	
All	rs1360780	TT, 104 (0.11)	TC, 437 (0.46)	CC, 412(0.432)	TT, 48 (0.12)	TC, 187 (0.45)	CC, 180 (0.434)	TT/TC, 0.93 (0.63-1.36)	TT/CC, 0.95 (0.64-1.39)	TC/CC, 1.02 (0.80-1.30)	0.93	n.s	
	rs4713916	AA, 79 (0.083)	AG, 386 (0.41)	GG, 489 (0.51)	AA, 33 (0.08)	AG, 140 (0.34)	GG, 243 (0.58)	AA/AG, 0.87 (0.55-1.37)	AA/GG, 1.18 (0.78-1.81)	AG/GG, 1.36 (1.07-1.74)	0.042	n.s	
	rs3800373	AA, 433 (0.462)	AC, 410 (0.437)	CC, 94 (0.10)	AA, 187 (0.455)	AC, 179 (0.436)	CC, 45 (0.11)	AA/AC, 1.01 (0.79-1.29)	AA/CC, 1.11 (0.74-1.65)	AC/CC, 1.10 (0.74-1.64)	0.88	n.s	
White n-H	rs1360780	TT, 69 (0.10)	TC, 314 (0.48)	CC, 278 (0.42)	TT, 28 (0.11)	TC, 104 (0.42)	CC, 116 (0.47)	TT/TC, 0.81 (0.49-1.35)	TT/CC, 1.03 (0.63-1.67)	TC/CC, 1.26 (0.92-1.72)	0.32	n.s	
	rs4713916	AA, 64 (0.10)	AG, 308 (0.47)	GG, 290 (0.44)	AA, 25 (0.10)	AG, 100 (0.40)	GG, 124 (0.50)	AA/AG, 0.83 (0.49-1.40)	AA/GG, 1.09 (0.66-1.80)	AG/GG, 1.32 (0.97-1.79)	0.21	n.s	
	rs3800373	AA, 304 (0.47)	AC, 283 (0.44)	CC, 61 (0.09)	AA, 122 (0.50)	AC, 101 (0.41)	CC, 23 (0.09)	AA/AC, 0.89 (0.65-1.21)	AA/CC, 0.94 (0.56-1.58)	AC/CC, 1.06 (0.62-1.80)	0.76	n.s	
Black	rs1360780	TT, 18 (0.15)	TC, 58 (0.48)	CC, 46 (0.38)	TT, 11 (0.14)	TC, 47 (0.61)	CC, 19 (0.25)	TT/TC, 1.32 (0.58-3.01)	TT/CC, 0.67 (0.26-1.71)	TC/CC, 0.52 (0.28-0.98)	0.13	n.s	
	rs4713916	AA, 0 (0.0)	AG, 23 (0.19)	GG, 98 (0.81)	AA, 0 (0.0)	AG, 12 (0.16)	GG, 65 (0.84)	n.a.	n.a.	AG/GG, 1.26 (0.60-2.67)	0.54	n.s	
	rs3800373	AA, 41 (0.34)	AC, 65 (0.53)	CC, 16 (0.13)	AA, 20 (0.26)	AC, 43 (0.56)	CC, 14 (0.18)	AA/AC, 1.35 (0.71-2.58)	AA/CC, 1.80 (0.73-4.42)	AC/CC, 1.32 (0.58-3.00)	0.41	n.s	

* frequencies in parentheses. a) Remitters vs. non-remitters. b) Responders vs non-responders.

Table 3

Results from allele-wise association tests for outcome in treatment-response in the total sample (all ethnicities) as well as sub-samples (White non-Hispanic and Black). The table also presents odds-ratio values (OR) as well as the upper (Hi) and lower (Lo) values from the 95% confidence interval (C.I.). Overall p-values from association tests are shown, both as nominal values and after correction for multiple testing (correction factor of 18) (n.s = not significant).

Table 3a									
Ethnic group	SNP	Remitter		Non-remitter		OR (C.I., Lo-Hi)		Nominal p-value	Corrected p-value
All	rs1360780	T, 496 (0.34)	C, 948 (0.66)	T, 307 (0.33)	C, 625 (0.67)	T/C, 1.01 (0.89-1.27)		0.48	n.s
	rs4713916	A, 433 (0.30)	G, 1013 (0.70)	A, 221 (0.24)	G, 713 (0.76)	A/G, 1.37 (1.14-1.65)		0.00074	0.013
	rs3800373	A, 959 (0.67)	C, 463 (0.33)	A, 629 (0.69)	C, 289 (0.31)	A/C, 0.95 (0.80-1.14)		0.59	n.s
White n-H	rs1360780	T, 353 (0.34)	C, 679 (0.66)	T, 170 (0.30)	C, 396 (0.70)	T/C, 1.21 (0.97-1.50)		0.088	n.s
	rs4713916	A, 354 (0.34)	G, 680 (0.66)	A, 157 (0.28)	G, 411 (0.72)	A/G, 1.35 (1.09-1.69)		0.0064	n.s
	rs3800373	A, 693 (0.68)	C, 321 (0.32)	A, 404 (0.72)	C, 156 (0.28)	A/C, 0.84 (0.67-1.05)		0.12	n.s
Black	rs1360780	T, 70 (0.40)	C, 104 (0.60)	T, 74 (0.45)	C, 92 (0.55)	T/C, 0.84 (0.54-1.29)		0.42	n.s
	rs4713916	A, 17 (0.10)	G, 157 (0.90)	A, 14 (0.08)	G, 152 (0.92)	A/G, 1.17 (0.56-2.46)		0.67	n.s
	rs3800373	A, 101 (0.58)	C, 73 (0.42)	A, 88 (0.54)	C, 76 (0.46)	A/C, 1.19 (0.78-1.84)		0.42	n.s
Table 3b									
Ethnic group	SNP	Responder		Non-responder		OR (C.I., Lo-Hi)		Nominal p-value	Corrected p-value
All	rs1360780	T, 654 (0.338)	C, 1261 (0.662)	T, 283 (0.341)	C, 547 (0.659)	T/C, 0.99 (0.83-1.17)		0.9	n.s
	rs4713916	A, 544 (0.29)	G, 1364 (0.72)	A, 206 (0.25)	G, 626 (0.72)	A/G, 1.21 (1.01-1.45)		0.042	n.s
	rs3800373	A, 1276 (0.68)	C, 598 (0.32)	A, 553 (0.67)	C, 269 (0.33)	A/C, 1.04 (0.87-1.24)		0.68	n.s
White n-H	rs1360780	T, 452 (0.34)	C, 870 (0.66)	T, 160 (0.33)	C, 336 (0.68)	T/C, 1.09 (0.88-1.36)		0.44	n.s
	rs4713916	A, 436 (0.33)	G, 888 (0.67)	A, 150 (0.30)	G, 348 (0.70)	A/G, 1.14 (0.91-1.42)		0.25	n.s
	rs3800373	A, 891 (0.69)	C, 405 (0.31)	A, 345 (0.70)	C, 147 (0.30)	A/C, 0.94 (0.75-1.17)		0.57	n.s
Black	rs1360780	T, 94 (0.39)	C, 150 (0.61)	T, 69 (0.45)	C, 85 (0.55)	T/C, 0.77 (0.51-1.16)		0.22	n.s
	rs4713916	A, 25 (0.10)	G, 219 (0.90)	A, 12 (0.08)	G, 142 (0.92)	A/G, 1.34 (0.67-2.68)		0.41	n.s
	rs3800373	A, 147 (0.60)	C, 97 (0.40)	A, 83 (0.54)	C, 71 (0.46)	A/C, 1.30 (0.86-1.95)		0.21	n.s

* frequencies in parentheses. a) Remitters vs non-remitters. b) Responder vs non-responders.