Single nucleotide polymorphisms (SNPs) in the ionotropic glutamate receptor GRIK4 and the serotonergic receptor HTR2A have been recently shown to be associated with symptoms after 5 weeks. We tested for association with response (50% reduction of the baseline score of the Hamilton Depression Rating Scale, HDRS) and remission (HDRS < 10) of depressive symptoms in the MARS project. In our study the choice of antidepressant drug was not restricted. We analyzed 82 SNPs within the GRIK4 locus and 38 SNPs within the HTR2A locus which we tested for association with response (50% reduction of the baseline score of the Hamilton Depression Rating Scale, HDRS) and remission (HDRS < 10) of depressive symptoms after 5 weeks.

**Background**

Despite large differences in study design and ethnicity, our results support an involvement of both GRIK4 and HTR2A in antidepressant treatment response. Our data show that these genes have both independent and interaction effects and suggest that considering a panel of SNPs for the prediction of treatment response will be necessary to predict treatment response in a manner that will be clinically relevant.

**Material & Methods**

We could replicate associations of the best GRIK4 and HTR2A SNP identified as predictors of treatment response in the STAR*D sample. However, while for the GRIK4 SNP the same allele associated with non-remission in our sample (rs1954787, one-sided p = .04), it was the complementary allele for rs7997012 in HTR2A (allelic, two sided, p = .043). The SNPs with the strongest association in the MARS sample, had not previously been reported in STAR*D. To assess the overall association of genetic variation in the investigated loci, we used the Fisher’s product method (FPM). This analysis identified a significant association with remission at 5 weeks for both genes (GRIK4, p = .029; HTR2A, p = .012). In a logistic regression analysis (n = 292) with the best GRIK4 SNP (rs12800734), HTR2A SNP (rs17288723) and rs1360780 in FKBP5, a gene associated with treatment response in STAR*D and MARS, as well as their two SNPs interaction terms, the best model included the main effects for rs17288723 and rs12800734, and in addition a significant interaction (p = .003) between rs12800734 (GRIK4) and rs1360780 (FKBP5). This 3 SNP model explained 15.7% of the variance for remission at 5 weeks and had a p-value < .0001. In an extended sample (n = 374) three additional SNPs had significant interaction effects: (1) between rs12800734 (GRIK4) and rs1360780 (FKBP5) (p = .005) and (2) between rs17288723 (HTR2A) and rs12800734 (GRIK4) (p = .028). This 3 SNP model explained 13.1% of the variance for remission at week 5 (p = .0001).

**Conclusion**

Despite large differences in study design and ethnicity, our results support an involvement of both GRIK4 and HTR2A in antidepressant treatment response. Our data show that these genes have both independent and interaction effects and suggest that considering a panel of SNPs for the prediction of treatment response will be necessary to predict treatment response in a manner that will be clinically relevant.