Gene expression as predictors of antidepressant response in the *GENDEP* study

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To improve the 'personalized-medicine' approach to the treatment of depression, we need to identify biomarkers that, assessed before starting treatment, predict future response to antidepressants. We tested the leukocyte mRNA expression levels of genes belonging to glucocorticoid receptor function, inflammation and neuroplasticity, in 34 healthy controls and 74 depressed patients, as part of the GENDEP study. We identified three pro-inflammatory cytokines as predictors of the treatment response. Indeed the expression levels of IL-1β, MIF and TNF-α at the baseline were all strongly and negatively correlated with treatment response (*IL-1β*, r=-0.56; *MIF*, r=-0.62; and *TNF*-α, r=-0.44; all p<0.0001). Moreover a linear regression analyses identified the best predictive model the one where the three cytokines were all included in the model, and accounted for the 46% of the variance in the treatment response.

In order to better evaluate the accuracy of these predictors, we have run a receiver operating characteristic (ROC) analysis. N=23 patients (31%) did not respond to antidepressants (escitalopram or nortryptiline), that is, did not show a reduction in MADRS score of 50% or more. Using 'lack of response' as positive actual state in the ROC analysis, four genes plotted above the reference line (that is, higher gene expression predicting lack of response) with areas under the curve (AUCs) that were indicative of at least 'fair' predictive value: MIF (0.9), IL-1β (0.8), TNF-α (0.8) and FKBP-5 (0.7). All the other genes had AUCs <0.7, indicating poor predictive values. Further analyses indicated that the expression values of these genes that had the best combination of sensitivity and specificity in predicting lack of response were: 1.35 for MIF, 1.56 for IL-1β, 1.55 for TNF-α, and 1.34 for FKBP-5. Our data suggest that monitoring the levels of these genes could identify depressed patients who are least likely to respond to first-line antidepressants, and this could allow doctors to consider early introduction of more assertive therapeutic approaches of combining antidepressants or adding adjuvant therapies.