Identifying transcriptomic biomarkers for the clinical response to escitalopram in the inflammatory cytokine pathway

Timothy R. Powell[1*], Leonard C. Schalkwyk[1], Andrew L. Heffernan[1], Gerome Breen[1], Timothy Lawrence[1], Tom Price[1], Anne Farmer[1], Katherine J. Aitchison[1], Ian Craig[1], Andrea Danese[1], Carmine Pariante[2], Cathryn Lewis[1], Peter McGuffin[1], Rudolf Uher[1], Katherine E. Tansey[1], and Ursula M. D'Souza[1]

[1] MRC *Social, Genetic and Developmental Psychiatry Research Centre, Institute of Psychiatry, King's College London, De Crespigny Park, London, UK.*

[2] *Centre for the Cellular Basis of Behaviour, The James Black Centre, King's College London, Coldharbour Lane, London, UK*

Introduction

▪Research shows an increase in proinflammatory cytokines, acute-phase proteins and chemokines are present in individuals suffering from depression (Miller et al., 2008).

▪Interestingly, antidepressants have anti-inflammatory properties (Roumestan et al., 2007) and evidence suggests that the inter-individual variability in response to antidepressants may reflect genetic differences in the inflammatory cytokine pathway (Uher et al., 2010).

▪In particular, the SNPs rs1126757 in interleukin-11 (*IL11*), and rs7801617 in interleukin 6 (*IL6*), and protein levels of Tumour Necrosis Factor (*TNF*) have previously been implicated in predicting the clinical response to the antidepressant escitalopram, a selective serotonin reuptake inhibitor (SSRI).

▪As opposed to genotype biomarkers, transcriptional biomarkers have the advantage of capturing the functional output of genotypes interacting with epigenetic and transcription factor binding; both of which have additionally been linked to antidepressant response (Cassel et al., 2006; Thome et al., 2000).

▪Identifying transcriptomic biomarkers at baseline is useful in patient-specific treatment selection. Investigating the gene expression effects of antidepressants after treatment in relation to clinical response is useful in understanding the mechanism of action of antidepressants and the cause if inter-individual variability.

▪ **The Aim of the current study was to investigate mRNA expression of *IL11, IL6* and *TNF* as well as genes in the wider inflammatory cytokine pathway in depressed patients who were either responders (n=25) or non-responders (n=21) to escitalopram using a subset of samples in the Genome-Based Therapeutic Drugs for Depression (GENDEP) project.**

Methods

- Clinical response was based on a percentage change in MADRS score over a 12 week treatment period with escitalopram.
- Blood was collected at baseline and after eight weeks of treatment with escitalopram.
- Expression of mRNA was assessed using the Human Inflammatory Cytokines and Receptors PCR Array (SABiosciences).

- The relative quantification method of normalisation was used which required the selection of appropriate reference genes using geNorm and Normfinder analyses.
- Differences between responders and non-responders were assessed using binary logistic regressions covarying for age, sex, centre of treatment and baseline MADRS score. Genotype differences were assessed using linear regressions covarying for age, sex and centre of treatment.
- Genes in the wider inflammatory cytokine pathway were treated in an *a priori* manner and underwent False Discovery Rate (FDR) of multiple correction.

Results

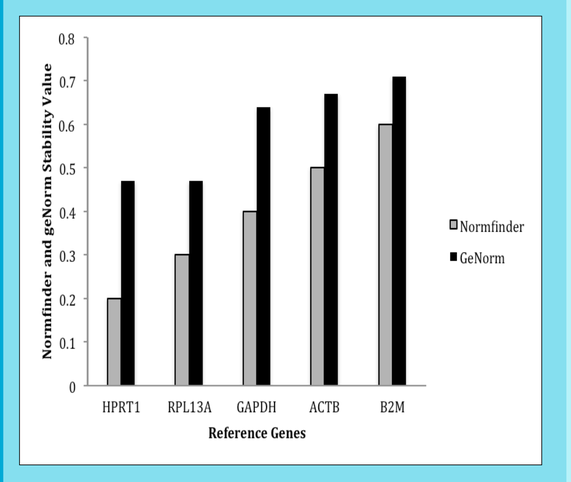


Fig. 1 Normfinder and GeNorm analyses reveal the three most stable reference genes in blood following escitalopram treatment are *HPRT1*, *RPL13A* and *GAPDH* .

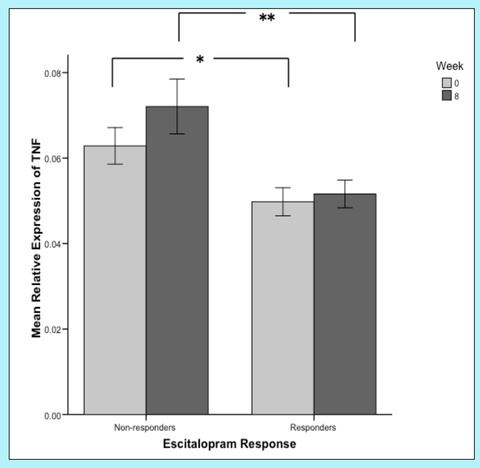
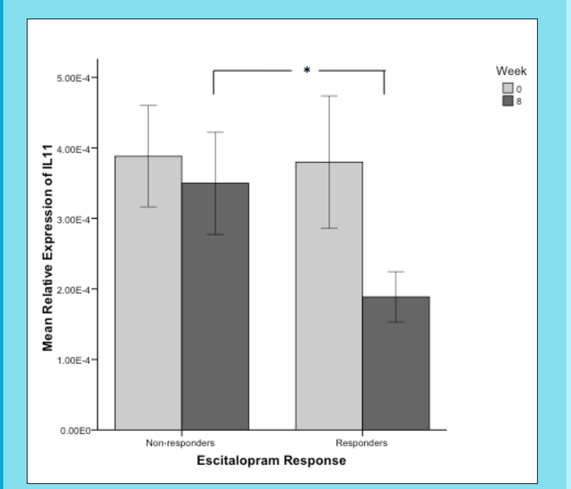


Fig. 2 Bar graph showing the mean relative expression of the target gene *TNF* in responder and non-responder groups at baseline (week 0) and after escitaloprm treatment (week 8). Significant differences of p≤0.01 are denoted by **.



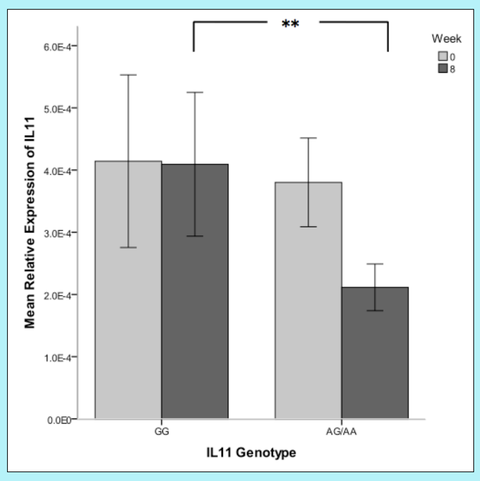


Fig. 3 (left) shows the differences between responsers and non-responders in the target gene *IL11,* p≤0.05 are denoted by *.

Fig. 4 (right) shows the differences in expression between carriers of the GG genotype (associated with non-response) compared to those carrying one or more copies of the A allele AA/ AG (associated with clinical response) of the rs1126757 SNP, p≤0.01 are denoted by ** .

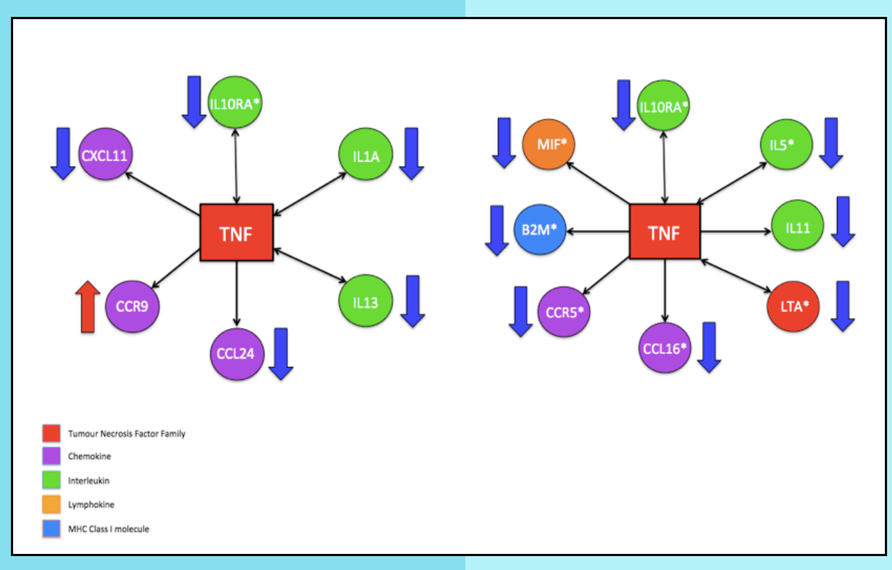


Fig. 5 depicts the top gene expression differences in the inflammatory cytokine pathway between responders and non-responders to escitalopram at baseline (left) and after eight weeks escitalopram treatment (right). Downward arrows represent lower expression in responders, upward arrows represent higher expression in responders.

Discussion

▪*.TNF* and its targets may act as putative transcriptomic biomarkers for the clinical response to escitalopram (Figs. 2 and 5). TNF has been previously shown to regulate serotonin synthesis (Miller et al., 2008), serotonin transporter gene expression (Zhu et al., 2006) and hippocampal neurogenesis (Monje et al., 2003), all relating the the believed therapeutic effects of antidepressants.

▪*IL11* shows differential expression between responders and non-responders but only after eight weeks of treatment with escitalopram (Fig. 3). Moreover, expression differences in IL11 were found to be mediated by genotype-specific expression changes relating to rs1126757 (Fig. 4), suggesting a functional role for this SNP in mediating escitalopram response.

▪Results confirm findings at the protein level which show that responders to antidepressants tend to show lower levels of inflammatory cytokines than non-responders (Tuglu et al., 2003), see Fig. 5.

▪This study provides strong support for the role of genetic differences in the inflammatory cytokine pathway in mediating response to escitalopram.

▪Results require replication in larger cohorts.

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