Polymorphisms in FKBP5 are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment.

Abstract:
The stress hormone-regulating hypothalamic-pituitary-adrenal (HPA) axis has been implicated in the causality as well as the treatment of depression. To investigate a possible association between genes regulating the HPA axis and response to antidepressants and susceptibility for depression, we genotyped single-nucleotide polymorphisms in eight of these genes in depressed individuals and matched controls. We found significant associations of response to antidepressants and the recurrence of depressive episodes with single-nucleotide polymorphisms in FKBP5, a glucocorticoid receptor-regulating cochaperone of hsp-90, in two independent samples. These single-nucleotide polymorphisms were also associated with increased intracellular FKBP5 protein expression, which triggers adaptive changes in glucocorticoid receptor and, thereby, HPA-axis regulation. Individuals carrying the associated genotypes had less HPA-axis hyperactivity during the depressive episode. We propose that
the FKBP5 variant-dependent alterations in HPA-axis regulation could be related to the faster response to antidepressant drug treatment and the increased recurrence of depressive episodes observed in this subgroup of depressed individuals. These findings support a central role of genes regulating the HPA axis in the causality of depression and the mechanism of action of antidepressant drugs.