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New biological pathways for major depression: gene expression decomposition in GxE components

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Major Depressive Disorder (MDD) is a common complex disabling psychiatric condition among the top five leading causes of disability throughout the world. Low heritability and high heterogeneity made the identification of genetic risk variants a challenging task. The aim of this study was to investigate genetically regulated gene expression in MDD, exploring how genetic and environmental factors (GxE) contribute to the disease. Our study exploits an innovative approach that involves the decomposition of gene expression levels in their two major components: an expression component regulated uniquely by genetic polymorphisms (GReX) and a component influenced by environmental factors (N-Gre). In this regard, we reanalyzed genotype and blood expression data of the Levinson s dataset (NIMH Study 88), that includes 463 MDD patients and 459 controls of European-ancestry. PrediXcan was used to estimate GReX in blood and in ten brain regions. N-Gre was computed in blood from the residuals of a linear regression model that correlates the observed gene expression levels with the predicted GReX levels.

After dissection of the blood gene expression levels in the GReX and N-GRe component, we noted that the major contribution to the gene expression differences observed in the original study among MDD and controls was due to the N-GRe component.

Gene-set enrichment analysis of the top hit DEGs emerged from analysis of the GreX component revealed a significant enrichment: 1) of genes involved in energy metabolism pathways, in blood; 2) of genes of the GO Cellular Component cilium , in the nucleus accumbens. These results suggest that polymorphisms in genes involved in the energy pathways as well in cilium components could be risk factors for MDD through a tissue specific modulation of gene expression.

In conclusion, the dissection of genetic expression levels in a GReX and N-GRe component could be a useful strategy to identify masked biological pathways that could be involved in the etiopathogenesis of MDD.