NEUROENDOCRINOLOGY

Metabolic syndrome in depression is linked to *TPH2*

Tryptophan hydroxylase 2 (TPH2) is a rate-limiting enzyme for brain 5-hydroxytryptamine biosynthesis, and has been associated in genetic studies with affective disorder spectrum diseases such as recurrent unipolar depression. Metabolic syndrome and major depression have strong comorbidity, which led Stefan Kloiber and colleagues from the Max Planck Institute of Psychiatry, Munich, Germany, to investigate whether specific genetic variants in the *TPH2* gene are associated with recurrent unipolar depression or metabolic syndrome, and whether these variants contribute to an elevated risk of metabolic syndrome in patients with recurrent unipolar depression.

> “These findings ...associate functional polymorphisms in *TPH2* with a decrease in central serotonergic activity characters...”

Kloiber's team recruited 988 patients with recurrent unipolar depression and matched them to 1,023 healthy individuals for ethnicity, sex and age. Patients with recurrent unipolar depression were more likely to have metabolic syndrome than were controls, and these differences were particularly marked in women. The researchers genotyped 41 single nucleotide polymorphisms (SNPs) throughout the *TPH2* gene in 300 patients with recurrent unipolar depression and in 300 controls. Two SNPs (rs7305115 and rs17110690), located in exon 7 and intron 8 of *TPH2*, respectively, were associated with the occurrence of metabolic syndrome in patients with recurrent unipolar depression. The researchers were able to replicate this finding for the SNP rs17110690 in a second sample, which consisted of the remaining 688 patients with recurrent unipolar depression and 723 controls. The risk of metabolic syndrome was most pronounced in patients who were homozygous for the G allele of rs17110690.

This work, alongside previous functional studies, links risk genotypes and risk haplotypes of rs17110690 to reduced cerebral *TPH2* mRNA expression and reduced 5-hydroxytryptamine levels in the CNS. These findings seem, therefore, to associate functional polymorphisms in *TPH2* with a decrease in central serotonergic activity, especially within a subgroup of patients with recurrent unipolar depression. These patients seem prone to develop metabolic disorders as a result of this genotype-dependent impairment.

“Our work [helps] to explain parts of the pathological mechanisms underlying the comorbidity of depressive and metabolic disorders,” says Kloiber, “and may facilitate early identification of depressive patients at risk for metabolic disorders in order to initiate personalized and individualized therapy”.

Mick Aulakh

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