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GLUTAMATE DECARBOXYLASE 1 DNA HYPOMETHYLATION - AN EPIGENETIC SIGNATURE OF PANIC DISORDER?

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The glutamate decarboxylase (GAD67/65; GAD1/GAD2) as the rate-limiting enzyme in gamma-aminobutyric acid (GABA) synthesis has been suggested as a prime candidate in the pathogenesis of anxiety disorders. In the present study, DNA methylation of GAD1/2 gene regulatory regions was investigated for association with panic disorder with particular attention to possible effects of environmental factors.

Sixty-five patients with panic disorder (f=44, m=21) and 65 matched healthy controls were analyzed for DNA methylation status at 40 GAD1 and 10 GAD2 CpG sites via direct sequencing of sodium bisulfate treated DNA extracted from blood cells. The occurrence of recent positive and negative life events was ascertained. Patients and controls were genotyped for GAD1 genetic variation.

Patients with panic disorder exhibited significantly lower average GAD1 methylation than healthy controls. The occurrence of negative life events was correlated with relatively decreased average methylation mainly in the female subsample. GAD1 SNPs rs3749034 and rs3762555 conferred a significantly lower methylation at three GAD1 CpG sites. No differential methylation was observed in the GAD2 gene.

The present pilot data suggest a - potentially compensatory - role of GAD1 gene hypomethylation in panic disorder possibly mediating the influence of negative life events and dependent on genetic variation. Future studies are warranted to replicate the present finding in independent samples, preferably applying a longitudinal design.

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