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IMPRINTING IN THE SCHIZOPHRENIA CANDIDATE GENE GABRB2

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Imprinting, characterized by unequal expression of the offspring's genes in a parent-of-origin dependent manner, has been functionally implicated in brain development and in psychiatric disorders. In this study, unambiguous distortion in paternal but not maternal transmission of the disease-associated single-nucleotide polymorphism (SNP) rs6556547 (T/G) clearly indicated the presence of parent-of-origin effect (POE) in the $GABA_A$ receptor β_2 subunit gene (GABRB2). 'Flipping' of allelic mRNA expression in heterozygotes of SNP rs2229944 (C/T) and the observed two-tiered distribution of mRNA expression levels in heterozygotes of the disease-associated SNP rs1816071 (G/A) furnished important support for the occurrence of imprinting at GABRB2. Imprinting in effect introduced heterozygotes from different parents-of-origin endowed with dissimilar mRNA expression capabilities. The deficit of upper-tiered expressions accounted for the lowered mRNA expression levels in the schizophrenic heterozygotes. This pointed to the necessity of differentiating between two kinds of heterozygotes of different parental origins in disease association studies on GABRB2. Bisulfite sequencing revealed hypermethylation in the neighborhood of SNP rs1816071, and methylation differences between controls and schizophrenia patients. Notably, allele-specific methylation was observed at the disease-associated SNPs rs6556547 and rs1816071. These findings raised the possibility that CpG methylation status of these sites could have an impact on the expression of GABRB2 and the risk of schizophrenia. Furthermore, the occurrence of imprinting and allele-specific methylation in the schizophrenia candidate gene GABRB2 was compatible with the epigenetic hypothesis for schizophrenia pathophysiology, thereby calling for the need to explore the role of epigenetic factors in mediating susceptibility to schizophrenia.

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