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AN ALTERNATIVE-SPLICING HOT-SPOT IN *GABRB2*: NOVEL SPLICING VARIANTS ASSOCIATED WITH MAJOR PSYCHOTIC DISORDERS

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GABRB2, the gene for β_2 subunit of the gamma-aminobutyric acid type A ($GABA_A$) receptor, is known to display two splicing isoforms in the brain, namely β_{2L} containing Exon 10 and β_{2S} devoid of Exon 10. Previously, the expressions of these isoforms were correlated with both schizophrenia and various sequence polymorphisms of the gene. In the present study, a series of deletions made on Intron 9 of a minigene construct affected the expression of Exon 10, and generated additional splicing variations suggesting the existence of additional splicing variants of β_2 subunit. A search among brain cDNAs uncovered the two novel short forms: β_{2S1} which is devoid of Exons 10 and 11 and bears an extended Exon 9, and β_{2S2} which is devoid of Exon 10 and bears a shortened Exon 11.Real-time quantitative polymerase chain reaction, performed with a cohort of 31 schizophrenics, 30 bipolar disorder and 31 controls of US population, showed that the level of β_{2S2} was significantly decreased in bipolar disorder, and marginally decreased in schizophrenia, while β_{2S1} was marginally increased in both of these psychotic disorders. Significant genotypic effects of rs1816071, rs1816072 and rs187269 on β_{2S2} level were observed in male schizophrenic and bipolar patients. These findings pointed to the neighborhood of Exon 10 as an alternate-splicing hot-spot, and underlined the relevance of β_2 subunit isoforms to the etiology of psychotic disorders.

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