Genetic Polymorphism in DTNBP1 Gene Is Associated With Methamphetamine-Induced Panic Disorder

Maw Shin Sim, PhD, Ahmad Hatim, MD, PhD, Shiau Hui Diong, MMedSci, and Zahurin Mohamed, PhD

Objective: The dysbindin-1 (dystrobrevin-binding protein-1 [DTNBP-1]) gene has repeatedly been shown to be associated with psychotic disorder across diverse populations. In this study, we attempted to investigate the association of the rs3213207 (P1635) genetic polymorphism of the DTNBP1 gene with methamphetamine dependence and with methamphetamine-induced psychosis, manic episodes, and panic disorder in a male Malaysian population.

Methods: This polymorphism was genotyped in 233 male methamphetamine-dependent subjects and in 301 male controls of the following 4 different ethnicities: Malay, Chinese, Kadazan-Dusun, and Bajau. Intergroup statistical analyses were performed by using the χ² test and the Fisher exact test where necessary. In cases of multiple comparisons, the Bonferroni correction was performed.

Results: Our results indicated that the DTNBP1 rs3213207 polymorphism did not show any significant association with risk of methamphetamine dependence, either in the pooled subjects or after stratification into the 4 different ethnic groups (P > 0.05). Furthermore, we did not find any association of this polymorphism with methamphetamine-induced psychosis and episodes of methamphetamine-induced mania. However, there was a strong association between this polymorphism and the occurrence of methamphetamine-induced panic disorder in the pooled subjects (odds ratio [OR] = 6.739, P < 0.001) and in the Malay (OR = 11.93, P = 0.022) and Kadazan-Dusun (OR = 115.0, P < 0.001) groups.

Conclusions: Our findings suggest that the DTNBP1 rs3213207 polymorphism may contribute to methamphetamine-induced panic disorder in the pooled Malaysian male population, especially in the Malay and Kadazan-Dusun ethnic groups. However, no association was found with methamphetamine dependence, methamphetamine-induced psychosis, or methamphetamine-induced mania.

Key Words: dystrobrevin-binding protein, mania episodes, methamphetamine dependence, panic disorder, psychosis, single-nucleotide polymorphism

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Methamphetamine is a central nervous system stimulant drug that is similar in structure to amphetamine. Because of its high potential for abuse, methamphetamine is classified as a Schedule II drug of the United Nations Convention on Psychotropic Substances treaty. Methamphetamine is a highly addictive drug of abuse (Volkow et al., 2001). It has become a popular recreational drug in recent years, and its abuse continues to be a growing problem worldwide. It was reported that 53% of global total methamphetamine users live in Asia (United Nations Office on Drugs and Crime, 2011). In Malaysia, the National Anti-Drug Agency (2010) reported that 3428 addicts were dependent on methamphetamine (January to October 2010), 9 times the number of addicts who were found to be dependent on it the previous year (January to October 2009).

Dysbindin-1 (dystrobrevin-binding protein-1 [DTNBP-1]) is a coiled-coil protein encoded by the DTNBP1 gene, which is located on chromosome 6p22.3 in humans. This protein is a neuronal protein that binds to α- and β-dystrobrevin in muscle and brain (Benson et al., 2001), which links the cytoskeleton to the extracellular matrix and serves as a scaffold for signaling proteins (Veroni et al., 2007). The first study regarding the association of the DTNBP1 gene with increased risk of schizophrenia was reported in an Irish population (Bhardwaj et al., 2009). Repeat performances of the schizophrenia study showed consistent findings in different populations—German (Schwab et al., 2003), Irish (Van Den Oord et al., 2003), Chinese (Tang et al., 2003), Swedish/German/Polish (Van Den Bogaert et al., 2003), UK/Irish (Van Den Bogaert et al., 2003), Bulgarian (Kirov et al., 2004), American (Funke et al., 2004), and Japanese (Numakawa et al., 2004), although the significantly associated alleles and haplotypes were not always consistent among populations. Two postmortem studies also revealed that dysbindin-1 protein or its mRNA level was reduced in the dorsolateral prefrontal cortex and in presynaptic glutamatergic terminals of