

## The HTR1B 861G > C receptor polymorphism among patients suffering from alcoholism, major depression, anxiety disorders and narcolepsy

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### Abstract

The HTR1B receptor gene has been linked to antisocial alcoholism in a Finnish population and an American Indian tribe [Lappalainen et al., Arch. Gen. Psychiatry, 55 (1998) 989]. Using a candidate gene approach, we genotyped 209 patients with alcoholism, 108 patients with major depression, 32 patients with panic disorder, 50 patients with generalized anxiety disorder, 58 patients with narcolepsy and 74 healthy volunteers for the HTR1B 861G > C polymorphism. There was a higher frequency of the HTR1B 861G alleles among the alcohol-dependent patients as compared to the control subjects ( $\chi^2 = 4.02$ , d.f. = 2,  $P = 0.04$ ). However, the association resulted from higher frequencies of the opposite alleles (HTR1B 861G), as originally reported by Lappalainen et al. (1998). Although the association in our study might be due to a type I error, the higher degree of HTR1B allele sharing within both populations could also argue for another alcoholism-relevant gene within the proximity of the HTR1B gene on human chromosome 6. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

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## 1. Introduction

Alterations of serotonergic neurotransmission have been described in a number of neuropsychiatric disorders, including alcoholism, anxiety disorders, major depressive disorder and narcolepsy (Benkert et al., 1993; Murphy et al., 1998). Molecular cloning has revealed a number of polymorphisms within the genes encoding the different serotonergic receptors (e.g. Lappalainen et al., 1995; Peroutka, 1998; Enoch and Goldman 1999). The human hydroxytryptamine 1B receptor gene (HTR1B) has attracted special attention, because animals without a functional HTR1B receptor show a number of interesting behavioral features linked to neuropsychiatric disorders (see Scarce-Levie et al., 1999, for review). Mice lacking the gene encoding for the HTR1B receptor display heightened aggressive behavior against new intruders (Saudou et al., 1994), are less sensitive to ethanol-induced ataxia (Crabbe et al., 1996, 1999; Phillips et al., 1999), and are more prone to the reinforcing effects of cocaine in a progressive ratio schedule (Rocha et al., 1998). The human HTR1B receptor is encoded by an intronless gene 1179 bp in length (Jin et al., 1992) located on human chromosome 6 (Lappalainen et al., 1995). A common *HincII* polymorphism (861G > C) in the human HTR1B gene was identified by Southern blotting–restriction digestion (Sidenberg et al., 1993), and independently by SSCP and PCR-RFLP methods (Lappalainen et al., 1995). The 861G > C polymorphism is in complete linkage equilibrium with another frequent nucleotide exchange at position 129 (129T > C) in this gene (Huang et al., 1999). Both polymorphisms do not alter the amino acid sequence of the HTR1B protein (Lappalainen et al., 1998; Huang et al., 1999). Intriguingly, the HTR1B 861G > C receptor polymorphism was linked to antisocial alcoholism in a Finnish sample and a sample derived from an American Indian tribe (Lappalainen et al., 1998).

In this study, we tested for association of the HTR1B 861G > C receptor polymorphism with the alcohol dependence phenotype in a clinical sample unselected for violent behavior. In addition,

we assessed the association between the HTR1B gene and temperament dimensions among the alcohol-dependent patients and healthy control subjects using the dimensional personality model developed by Cloninger and colleagues (Cloninger, 1987; Cloninger et al., 1995).

We expanded this investigation to other psychiatric disorders also linked to diminished serotonergic function, including major depression, generalized anxiety disorder, panic disorder and narcolepsy.

## 2. Methods

### 2.1. Subjects and clinical data

Participants were 209 (158 male and 51 female) patients with alcohol dependence, 108 (24 male and 84 female) patients with major depressive disorder, 32 (13 male and 26 female) patients with panic disorder without agoraphobia, 50 (16 male and 34 female) patients with generalized anxiety disorder, 58 (21 male and 37 female) patients with narcolepsy and 74 (52 male and 22 female) healthy control subjects. The alcohol-dependent patients were recruited as inpatients after detoxification in the Department of Psychiatry at the University of Mainz, Germany. The diagnosis of alcohol dependence was based on DSM-IV (1994) criteria and was made by an experienced clinical psychiatrist (A.S., I.A., and C.J.K.). Detailed data on additional DSM-IV axis I disorders were obtained from 107 alcohol-dependent patients using the composite international diagnostic interview (CIDI) by Wittchen and co-workers (Wittchen et al., 1998). Comorbid axis II disorders were evaluated among these patients using a structured clinical interview for DSM-IV axis II disorders (SCID II) (Williams et al., 1992). In addition, 63 male alcohol-dependent patients completed the temperament and character inventory (TCI) developed by Cloninger and colleagues (Cloninger, 1987; Cloninger et al., 1995; Richter et al., 1998).

The patients with anxiety disorders were included as outpatients taking part in Germany-wide

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