THE TAQI DRD2 A1 ALLELE IS ASSOCIATED WITH ALCOHOL-DEPENDENCE
ALTHOUGH ITS EFFECT SIZE IS SMALL

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Abstract — Background: Numerous studies of the relationship between the TaqIA DRD2 A1 allele and alcohol-dependence have been performed and many of these have shown an association whereas others have not (Noble, 2003). This has consequently generated some controversy as to whether such an association actually exists. In two recent meta-analyses on this topic (Noble, 2003; Young et al., 2004), both of which showed significant associations between the DRD2 A1 allele, and alcoholism and substance misuse, some important methodological issues have been discussed, which need to be addressed in forthcoming studies. Thus, the sample size is of great importance. In case–control studies it has been estimated that to detect the role of genes with small effect size of ~2, which is in the range of the DRD2 A1 allele–alcoholism relationship, case–control sets of 300–400 subjects are necessary (Noble, 2003). Methods: In the present study, we have consequently recruited a large number of subjects, 375 alcohol-dependent individuals, who were treated as inpatients for alcohol withdrawal symptoms and out of these 357 could be evaluated. As controls, 578 individuals screened and 254 individuals unscreened for alcohol consumption were used. Thus, the total number of subjects was 1217. Results: In the present study, in which the Taq IA/A2 DRD2 polymorphism was in Hardy–Weinberg equilibrium in the patient group and the two control groups, we found that the Taq DRD2 A1/A2 genotype frequency differed significantly between the alcohol-dependent group and both the total and screened control groups. Furthermore, the Taq DRD2 A1 allele frequency was significantly overrepresented in the alcohol-dependent subjects as compared with both the total and screened control groups. The odds ratio for alcohol-dependency being associated with the A1 allele was 1.34. Conclusions: Consequently, the findings in this study lend further support to the notion of an association between the DRD2 A1 allele and alcohol-dependence, although the effect size of the DRD2 A1 allele is small.

INTRODUCTION

More than a decade ago Blum et al. (1990) reported an association of the TaqIA dopamine D2 receptor (DRD2) A1 allele with severe alcoholism. Thereafter, numerous studies have been published and several of them have shown an increase of the DRD2 A1 allele frequency and prevalence, particularly in more severe forms of alcoholism (Noble, 2003). However, several other studies have shown no evidence for linkage or association of the DRD2 A1 allele with alcohol-dependence (Noble, 2003), including severe forms as assessed by the number of DSM-IV criteria (American Psychiatric Association, 1994) for the diagnosis of alcohol-dependence (Gelernter and Kranzler, 1999). It has been suggested that the association may rather be attributable to population stratification in some samples (Blomqvist et al., 2000). It should also be emphasized that the concept of severity of alcoholism varies considerably between different studies. In most studies, using a severity concept of alcoholism focusing on medical illness, an increased frequency of the DRD2 A1 allele has indeed been reported (Noble et al., 1994; Gorwood et al., 2000; Noble et al., 2000, Noble, 2003). In addition, Blum et al. (1991) have reported an increased frequency in subjects with depressive symptoms.

Consequently, whereas many studies have shown an association of the DRD2 A1 allele with alcoholism others have not. This has generated some controversy as to whether such an association actually exists. In two recent meta-analyses on this topic (Noble, 2003; Young et al., 2004), both of which...
performed in controls with European background from the United States, Europe, and Australia, have shown no significant variation in DRD2 A1 allele frequency among them (Noble, 2003).

The main aim of the present study was, thus, to recruit a large number of subjects to ensure that this study had the statistical power to detect the small effect size of the DRD2 A1 allele in its potential relationship with alcohol-dependence. The included alcohol-dependent subjects were treated as inpatients for alcohol withdrawal and had a high co-morbidity for somatic as well as psychiatric disorders. Unscreened as well as screened controls were included, enabling comparisons between alcohol-dependent subjects and both types of controls. In addition the A1 allele frequency and TaqI A1/A2 DRD2 genotypes could be compared between these two control groups.

We also investigated alcohol-dependent subjects grouped according to the three TaqIA genotypes of the DRD2. Alcohol and non-alcohol-related psychiatric and somatic diagnoses as well as histories of earlier psychiatric and somatic treatment occasions were compared between these three genotype groups. Thus, another aim of the present study was to investigate whether carriers of the DRD2 A1 allele, i.e. individuals with the genotypes A1/A1 and/or A1/A2, had a higher prevalence of alcohol-related and non-alcohol-related psychiatric and somatic diagnoses and histories of earlier psychiatric and somatic treatments. The rationale for this part of the study was that an increased frequency of the DRD2 A1 allele has earlier been reported in alcohol-dependent subjects with concomitant somatic and psychiatric disorders (see above). It should be noted that the frequency of the genotype A1/A1 is low in alcohol-dependent subjects as well as controls, ~3–4% (Noble, 2003), and consequently also in this part of the study, a relatively large number of alcohol-dependent subjects must be recruited to enable comparisons between the three genotypes of the DRD2. Finally, all recruited subjects were of Scandinavian and thus of European or Caucasian background and population stratification was, thereby, avoided.

METHODS

Patients

Female and male unrelated Caucasian patients of Scandinavian origin >20 years of age and consecutively admitted to an alcohol and drug treatment unit at the psychiatric department of a University hospital were included in the study. They had to fulfil DSM-IV criteria for alcohol-dependence (American Psychiatric Association, 1994) according to diagnoses from previous hospital records and/or assessments at time of admittance. The reasons for admittance were generally long-term periods of heavy alcohol consumption necessitating treatment for alcohol withdrawal symptoms.

Establishing of hospital records

On the day after admission, and when a psychiatrist had examined the patients psychiatrically and physically, a hospital record was established or new data added into earlier established records. Information of alcohol and drug intake, psychiatric or somatic treatments prior to admission was recorded and patients were asked whether treatments had occurred previously in other hospitals. Copies of records from other hospitals were collected and relevant data added to the patient’s record. After discharge, mostly after a treatment period of 5–6 days, diagnoses and information about the latest admission were also added and registered.

Examinations of the hospital records

An independent experienced investigator performed all examinations of the hospital records. The following data for each patient were collected: diagnoses according to ICD-10 (World Health Organization, 1992) of alcohol withdrawal states, alcohol-related psychiatric disorders during withdrawal, other psychoactive substance use disorders, non-alcohol-related psychiatric disorders, somatic disorders, and number of admissions in psychiatric and somatic hospitals, and other addiction treatment units. Furthermore, data from the present treatment period were collected for the following laboratory parameters: sedimentation rate, c-reactive protein, haemoglobin, mean corpuscular volume, leucocyte particle concentration, thrombocyte particle concentration, glucose, sodium, potassium, calcium, creatinine, albumin, bilirubin, alkaline phosphatase, alanine transferase, aspartate transferase, gamma-glutamyltransferase, carbohydrate deficient transferrin, amylase, urine protein, urine glucose, urine ketone, urine nitrites, and urine haemoglobin. Values for systolic and diastolic blood pressure levels at admission (day 1 after end of alcohol intake) and at discharge (day 5 or 6 after end of alcohol intake) were also collected. Blood pressure levels were measured by the use of a mercury sphygmomanometer after 10 min of rest in supine position.

Unscreened and screened controls

As unscreened controls 264 unrelated Caucasian subjects of Scandinavian origin were recruited from groups of healthy blood donors, patients with minor surgery, and other healthy volunteers. The subjects were only asked about their alcohol consumption in non-structured interviews. No rating scales for alcoholism were used. To be included the subjects should have no histories of medical or psychiatric disorders, including substance abuse/dependence.

Screened controls (n = 578; women: n = 168; men: n = 410) were obtained from a sample of 10 000 randomly selected individuals in the western part of Sweden (Västra Götaland region). The original sample of 10 000 individuals has been used in a population study of blood lipid levels, blood pressure, alcohol, and smoking habits (Berg et al., 2005). Out of this original sample 578 individuals also volunteered to donate blood samples for genotyping. All the 578 subjects were of Scandinavian origin and their mean age ± SD was 61 ± 8 years (range: 31–75). To be included in this study the subjects should have no histories of medical or psychiatric disorders, including substance abuse/dependence. The reported weekly alcohol consumption was 101 ± 133 g of pure alcohol (women: 53 ± 74; men: 121 ± 147).

Both control groups were used only for comparison of the DRD2 allele and genotype frequencies with those of the alcohol-dependent patients. Therefore background data for the control groups are reported only to a limited extent.
Genotyping
The DRD2 TaqI PCR was performed as described by Grandy et al. (1993) with minor modifications. In short, genomic DNA was extracted from venous blood samples, and the DRD2 gene was amplified by PCR using the primers 5’CCGTCGACGCTGGCCAAATGTATCA and 5’CCGTCGACCGTCTGAGCTCATCA. The 310 bp PCR product was cleaved with TaqI, resulting in cleavage of the DRD2-A2 allele into two fragments of 180 and 130 bp, while the DRD2-A1 allele was not cleaved (Eriksson et al., 2000).

Statistical analyses
TaqI DRD2 allele and genotype frequencies were compared between the three groups (patients, unscreened, and screened controls) using χ²-test. The patients were also sub-grouped into the three DRD2 genotypes (A1/A1, A1/A2, A2/A2). Differences in clinical characteristics between the three groups of genotypes in the patients were analysed by use of Student’s t-test or χ²-test. Correction according to Bonferroni was not considered necessary since only one polymorphism (TaqI A1/A2 DRD2) was studied, and, thus, there was no resampling of the same pool (Buckland, 2001). Effects of gender were analysed using χ²-test. The data are presented as mean ± standard deviation (SD).

This study was approved by the Ethics Committee of the Göteborg University, Sweden, and was in compliance with the Helsinki Declaration of 1975. Informed consent was obtained from all subjects. None of the subjects were paid for their participation in the study.

RESULTS

Subjects
In total, 375 alcohol-dependent patients, consecutively admitted for treatment of alcohol withdrawal symptoms, were included in the study. At the time of examination of the hospital records, data from 18 patients had to be excluded, either because of missing data in records (n = 14) or because of inaccurate diagnoses of alcohol dependence (n = 4). Thus, the study sample comprised of 357 patients, 66 females (18%) and 291 males (82%). The mean age of the patient group was 49 ± 10 (23–78) years [females 48 ± 9 (25–73) and males 49 ± 11 (23–78) years; ns].

Comparison between the patient and control groups
The genotype and allele frequencies for alcohol-dependent patients and controls (total group of controls, screened and unscreened controls, respectively) are shown in Table 1. The observed genotype frequencies did not deviate significantly from the expected frequencies, either in the patient (P = 0.984) or control (P = 0.986) groups. Hence, the TaqI A1/A2 DRD2 polymorphism was in Hardy–Weinberg equilibrium.

The TaqI DRD2 A1/A2 genotype frequency differed significantly between the alcohol-dependent group and both the total (P = 0.027) and the screened (P = 0.026) control groups. Furthermore, the TaqI DRD2 A1 allele frequency was significantly overrepresented in alcohol-dependent subjects as compared with both the total (P = 0.007) and the screened (P = 0.007) control groups (Table 1). The odds ratio for alcohol-dependency being associated with the A1 allele was 1.34 (95% CI: 1.08–1.67, P = 0.007; Table 2).

Comparisons within the patient group when sub-grouped according to genotype
The mean age for the three genotype groups was: for the A1/A1 group 46 ± 8 (31–58) years [female 48 years and 16 males 46 ± 8 (31–58) years], for the A1/A2 group 49 ± 10 (24–72) years [22 females 45 ± 10 (25–70) and 103 males 50 ± 10 (24–72) years], and for the A2/A2 group 49 ± 11 (23–78) years [42 females 49 ± 9 (31–73) and 173 males 49 ± 11 (23–78) years]. No significant differences in age were observed between the three genotype groups.

The duration of alcohol-dependence was >10 years in 287 patients (84%; 43 females and 244 males), whereas 55 patients (16%; 19 females and 36 males) had duration <10 years (data missing for 3 females and 12 males). In the A1/A1 group, 12 patients (80%; all males) had duration of alcohol-dependence >10 years and 3 patients (20%; 1 female and 2 males) had duration <10 years (data missing for two males). In the A1/A2 group, 103 patients (89%; 12 females and 91 males) reported duration >10 years and 13 patients (11%; 7 females and 6 males) reported duration <10 years (missing data on 3 females and 6 males). In the A2/A2 group,
172 patients (82%; 31 females and 141 males) had duration >10 years and 38 (18%; 8 females and 30 males) had duration <10 years (data missing in 3 female and 2 males). There was no difference in duration of alcohol-dependence between the three genotype groups.

Diagnoses of alcohol-related psychiatric disorders during withdrawal

Of 357 patients, 93 (26%; 14 females and 79 males) had, besides alcohol withdrawal syndrome per se, one or more additional diagnoses of alcohol-related disorders during withdrawal, according to ICD-10 (see Table 3). Thus, in the A1/A1 group nine patients (53%; all males) had any of these diagnoses, in the A1/A2 group 21 (17%; 4 females and 17 males) had one of these diagnoses, and in the A2/A2 group 63 (29%; 9 females and 54 males) had one of these diagnoses. A significant overall effect of the DRD2 genotype was found ($\chi^2 = 14.48, P < 0.001$). Further analysis showed significant differences between A1/A1 and A1/A2 ($\chi^2 = 12.56, P < 0.001$) and between A1/A2 and A2/A2 ($\chi^2 = 8.05, P < 0.01$). There was also a difference between A1/A1 and A2/A2 ($\chi^2 = 3.92, P < 0.05$).

Number and proportions (%) of patients with different diagnoses of alcohol withdrawal-related disorders are shown for the A1/A1, A1/A2, and A2/A2 genotypes in Table 3. For the diagnosis alcohol withdrawal-related ‘psychotic disorder’, an overall significance was seen among the three genotype groups ($\chi^2 = 6.39, P < 0.05$). Pairwise comparisons showed differences between A1/A1 and A1/A2 ($\chi^2 = 6.35, P < 0.02$), and between A1/A1 and A2/A2 ($\chi^2 = 4.79, P < 0.03$). For the diagnosis alcohol withdrawal-related ‘other mental and behavioral disorders’ a significant overall effect of the DRD2 genotype was observed ($\chi^2 = 7.38, P < 0.03$), with a significant difference between A1/A1 and A1/A2 ($\chi^2 = 8.01, P < 0.01$). No differences were observed between the three groups for the diagnoses alcohol withdrawal state with delirium and ‘amnesic syndrome’.

Diagnoses of other psychoactive substance use disorders

Of the 357 patients 92 (26%; 14 females and 78 males) had one or more diagnoses of psychoactive substance use (see Table 4) besides alcohol-dependence. In the A1/A1 group 7 patients (41%; 1 female and 6 males) had such diagnoses, in the A1/A2 group 28 (22%; 4 females and 24 males), and in the A2/A2 group 57 (27%; 9 females and 48 males). The proportion of patients with any of these diagnoses did not differ between the three groups. The patients were not assessed for nicotine-dependence.

When analysing the different diagnoses separately, a significant overall effect of DRD2 genotype on the diagnosis ‘stimulant abuse/dependence’ (amphetamine) was found ($\chi^2 = 6.90, P < 0.04$; see Table 4). Pairwise comparisons showed significant differences between A1/A1 and A1/A2 ($\chi^2 = 6.65, P < 0.01$), and between A1/A1 and A2/A2 ($\chi^2 = 5.03, P < 0.03$).

Non-alcohol-related psychiatric diagnoses

Of the 357 patients, 188 (53%; 40 females and 148 males) were registered for psychiatric diagnoses besides those associated with alcohol-dependence and withdrawal. A total of 14 patients (82%; 1 female and 13 males) in the A1/A1 group, 55 (44%; 10 females and 45 males) in the A1/A2, and 119 (55%; 29 females and 90 males) in the A2/A2 group had such diagnoses. The proportion of psychiatric diagnoses among the three groups showed a significant overall effect of the DRD2 genotype ($\chi^2 = 10.18, P < 0.01$). Pairwise comparisons showed significant differences between A1/A1 and A1/A2 ($\chi^2 = 8.81, P < 0.01$), and between A1/A1 and A2/A2 ($\chi^2 = 4.84, P < 0.03$).

Treatment occasions in psychiatric hospitals

A total of 353 patients (data on four males in the A1/A2 group missing) had been treated at psychiatric wards in different hospitals. Thus each patient, regardless of genotype or gender, had been subjected to such treatment earlier. There were no differences in number of treatments between the three genotype groups.

Treatment occasions in homes for addiction

Of 352 patients, 131 (37%; 15 females and 116 males; data missing for 1 female and 4 males) had earlier been treated for drug problems in homes for addiction. In the A1/A1 group five patients (29%; 1 female and 4 males) had undergone such treatment, in the A1/A2 group 43 (36%; 4 females and 39 males; data missing on 1 female and 3 males), and in the A2/A2 group 83 (39%; 10 females and 73 males; data missing on 1 male patient). The proportion of treated patients did not differ between the three genotype groups.
Somatic diagnoses
Of 357 patients, 238 (67%; 35 females and 203 males) had concomitant somatic diagnoses. In the A1/A1 group 12 patients (71%; 1 female and 11 males) had such diagnoses, in the A1/A2 group 85 (68%; 14 females and 71 males), and in the A2/A2 group 141 (66%; 20 females and 121 males). The proportion of patients with any of these somatic diagnoses did not differ between the three genotype groups. Neither were any differences found when analysing each somatic diagnosis group separately.

Treatment occasions in somatic hospitals
Of 352 patients, 67 (19%; 4 females and 63 males; data missing on 1 female and 4 males) had earlier been treated at somatic wards in different hospitals. Thus, in the A1/A1 group four patients (24%; all males) had undergone such treatments, in the A1/A2 group 32 (26%; 3 females and 29 males; data missing for 1 female and 3 males), and in the A2/A2 group 30 (14%; 2 females and 28 males; data missing on 1 male). A significant overall effect of the DRD2 genotype was found ($\chi^2 = 8.31, P < 0.02$). Further analyses showed only a significant difference between A1/A2 and A2/A2 ($\chi^2 = 8.17, P < 0.01$).

Laboratory parameters in the patient group
Several parameters showed values besides the normal laboratory ranges (data not shown). However, no significant differences were found in any of the laboratory parameters between the three genotype groups.

Blood pressure levels in the patient group
After end of alcohol intake (day 1) there were no differences in blood pressure levels between the three genotype groups (see Table 5). A trend for higher systolic blood pressure levels in A1/A1 in comparison with A2/A2 was found at discharge, 5–6 days after end of alcohol intake (A1/A1: 134 ± 20; A2/A2: 123 ± 17; $P = 0.05$). The diastolic blood pressure levels at discharge were significantly higher for the genotype A1/A1 compared with A2/A2 (A1/A1: 85 ± 12; A2/A2: 77 ± 11; $P < 0.03$).

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>A1/A1 (n = 15)</th>
<th>A1/A2 (n = 102)</th>
<th>A2/A2 (n = 174)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (Day 1)</td>
<td>139 ± 21</td>
<td>139 ± 22</td>
<td>140 ± 23</td>
</tr>
<tr>
<td>Diastolic blood pressure (Day 1)</td>
<td>88 ± 19</td>
<td>85 ± 14</td>
<td>86 ± 14</td>
</tr>
<tr>
<td>Systolic blood pressure (Day 5–6)</td>
<td>134 ± 20 (n = 12) 126 ± 21 (n = 90) 123 ± 17 (n = 149)</td>
<td></td>
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</tr>
<tr>
<td>Diastolic blood pressure (Day 5–6)</td>
<td>85 ± 12 (n = 12) 79 ± 12 (n = 90) 77 ± 11 (n = 149)</td>
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</tbody>
</table>

Table 5. Patients with alcohol-dependence sub-grouped according to the genotypes of DRD2

Shown are systolic and diastolic blood pressures (mmHg) at day 1 after end of alcohol intake and at discharge (day 5–6). Blood pressure levels are given as mean ± SD. Some patients dropped out during treatment and this explains the differences in n between the two time points. For significant differences see text.

Gender effects
There was a significant higher proportion of men with the diagnosis ‘stimulant abuse/dependence’ compared with women ($\chi^2 = 4.04, P < 0.05$). Also a higher proportion of men who had somatic diagnoses ($\chi^2 = 8.71, P < 0.01$) was found, with main differences for the following diagnose groups: tumours, neurological, gastrointestinal, and musculoskeletal diseases (data not shown). Higher proportion of men reported somatic hospital treatments ($\chi^2 = 8.86, P < 0.01$) and treatment occasions in homes for addiction ($\chi^2 = 5.41, P < 0.02$).

DISCUSSION
Numerous studies of the relationship between the TaqIA DRD2 A1 allele and alcohol-dependence have been performed and many of these have shown an association, whereas others have not (Noble, 2003). This has, consequently, generated some controversy as to whether such an association actually exists (Noble, 2003). In the two recent meta-analyses by Noble (2003) and Young et al. (2004) some very important methodological issues have been discussed, which need to be addressed in forthcoming studies. Thus, the sample size is of great importance. In case–control studies it has been estimated that to detect the role of genes with small effect size of ~2, which is in the range of the DRD2 A1 allele–alcoholism relationship, case–control sets of 300–400 subjects are necessary (Noble, 2003). It is noteworthy that in the meta-analyses of case–control association studies by Noble (2003) and Young et al. (2004) no individual study appears to include more than a total number of subjects (cases and controls) of about 500. Thus, the notion of an association between the DRD2 A1 allele and alcohol-dependence relies very much on findings in meta-analyses such as those of Noble (2003) and Young et al. (2004). The results of meta-analyses may, however, be associated with short-comings. For example, it is not necessarily true that averaging the averages of different populations gives the average of the combined population and instead some form of weighted paired analyses is required (Buckland, 2001). Therefore, there still seems to be a need for individual studies comprising a larger number of subjects to ensure that they have the statistical power to detect the small effect size of the DRD2 A1 allele in its potential relationship with alcohol-dependence. In the present study, we have consequently recruited a large number of subjects, 375 alcohol-dependent individuals, who were treated as inpatients for alcohol withdrawal symptoms and out of these 357 could be evaluated. As controls, 578 individuals screened and 264 individuals unscreened for alcohol consumption were used. The total number of subjects was, thus, 1217. In the present study, in which the TaqIA A1/A2 DRD2 polymorphism was in Hardy–Weinberg equilibrium in the patient group and the two control groups, we found that the TaqI DRD2 A1/A2 genotype frequency differed significantly between the alcohol-dependent group and both the total and screened control groups. Furthermore, the TaqI DRD2 A1 allele frequency was significantly overrepresented in the alcohol-dependent subjects as compared with both the total and screened control groups. The odds ratio for alcohol-dependency being
associated with the A1 allele was 1.34. Consequently, the findings in this study lend further support to the notion of an association between the DRD2 A1 allele and alcohol-dependence, although the effect size of the DRD2 allele is small.

All patients in the present study were admitted to hospital for treatment of alcohol withdrawal symptoms. A majority of the patients had duration of alcohol-dependence >10 years. In addition, one-fourth of the patient group had earlier and/or present diagnoses of other psychoactive substance use disorders (nicotine-dependence was not assessed). Besides alcohol withdrawal states, about one-fourth had alcohol-related psychiatric disorders during withdrawal. Slightly more than half of the patient group was furthermore found to have earlier and/or present psychiatric diagnoses unrelated to alcohol-dependence. Every one of the patients had earlier been admitted once or several times to psychiatric hospitals and a third of them had also been treated in homes for addiction. Furthermore, the majority (about two-third of the patients) had also one or several somatic diagnoses. On the other hand, only ~20% of them had earlier been referred to somatic hospitals, indicating that their reported somatic disorders were possibly not of such severity requiring somatic inpatient treatments. If to develop alcohol withdrawal symptoms, necessitating in-patient treatment, and to have high co-morbidity for somatic (67%) and psychiatric (53%) disorders are taken as indices for severity, the present group of subjects could be considered as having a severe form of alcohol-dependence. Consequently, the findings in the present study also support the notion of an increase in the DRD2 A1 allele frequency, particularly, in more severe forms of alcohol-dependence.

In the present study, we found no difference between controls screened or unscreened for alcohol consumption. This finding is in agreement with that of Gerlenter and Kranzler (1999) but at variance with the findings in the meta-analyses of Noble (2003) and Young et al. (2004), reporting lower prevalence and frequency of the A1 allele in screened in comparison with unscreened controls. The reason for this latter difference may be because in the present study the screened controls were registered only for alcohol consumption and not for nicotine or other drug abuse/dependence which was, on the other hand, the case in at least some of the studies included in the aforementioned meta-analyses.

In the second part of the study alcohol-dependent subjects were grouped according to the three TaqIA genotypes of the DRD2. Thereafter alcohol and non-alcohol-related psychiatric and somatic diagnoses and treatment occasions were compared between the three genotypes. The main findings from this part of the study were that alcohol-dependent subjects with the genotype A1/A1 had higher co-morbidity for alcohol-related psychiatric disorders during withdrawal, amphetamine abuse/dependence, and non-alcohol-related psychiatric disorders. It is, however, of importance that the genotype A1/A1 is rare in alcohol-dependent individuals as well as in the general population, ~3–4% (Noble, 2003). Therefore, the number of subjects in this genotype group was small and calculations of frequencies will be very susceptible to small fluctuations in case numbers. Consequently, the findings in this part of the study have limitations due to the small number of subjects in the A1/A1 genotype group. The findings in this part of the study should therefore be interpreted with caution.

There was no difference in somatic diagnosis or in laboratory parameters between the three genotype groups. However, alcohol-dependent subjects with the genotypes A1/A1 and A1/A2 had more treatment occasions in somatic hospitals. This latter finding may lend additional support to the notion that the A1 allele is overrepresented in alcohol-dependent subjects with more severe concomitant medical illnesses.

Finally, in this part of the study we also found that patients with the genotype A1/A1 had higher levels of systolic and diastolic blood pressure at discharge (5 or 6 days after end of alcohol intake). Since alcohol withdrawal-related hypertension abates after 5–6 days (Baldin et al., 1992, Fahlke et al., 2000), this finding suggests an association between this genotype and non-alcohol-related hypertension. It is of note that such an association between the Taq1 A1 allele of the DRD2 and hypertension has been reported also in obese individuals without alcohol-dependence (Fang et al., 2005).

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