GENETICS AND CELL BIOLOGY

Do Alcohol-dependent Individuals with DRD2 A1 Allele Have an Increased Risk of Relapse? A Pilot Study

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(Received 1 December 2010; in revised form 7 April 2011; accepted 12 April 2011)

Abstract — Aims: The TaqIA polymorphism of the dopamine D2 receptor (DRD2) gene has been extensively studied in relation to alcoholism, and the TaqIA A1 allele appears to be over-represented in alcohol-dependent individuals. In a recent study, this allele has also been associated with a highly increased mortality rate in alcohol-dependent individuals. In the present study, we investigated whether the TaqIA A1 allele of the DRD2 gene region was associated with a higher relapse rate in alcohol-dependent individuals.

Methods: Adult women (n = 10) and men (n = 40) with a diagnosis of alcohol-dependence were recruited from two Swedish 12-step treatment units for alcoholism. Subjects were genotyped for the TaqIA polymorphism. On average, 1½ year after the end of the treatment program, subjects were re-interviewed by using the alcohol-related items from the Addiction Severity Index follow-up version.

Results: Thirty-three (66%) subjects self-reported relapse and 17 (34%) abstinence during the follow-up period. Thirty-six percent (18/50) were carriers of the A1 allele of the DRD2 gene region, and 64% (32/50) were non-carriers. Among the carriers of the A1 allele, 89% (16/18) reported relapse in contrast to 53% (17/32) in the non-carriers (P = 0.01; odds ratio = 7.1). Conclusion: The present study is, to our knowledge, the first report of an association between the TaqIA A1 allele and a substantially increased relapse rate. It should be emphasized that the number of subjects is relatively small, and this investigation should therefore be considered as a pilot study.

INTRODUCTION

Previous research has demonstrated the effectiveness of treatment for alcohol-use disorders (AUDs)—i.e. alcohol-dependence or abuse. Relapse after treatment is, however, still frequent. There is no consensus in research today about an exact relapse rate, but the risk to resume drinking within a 12-month period after treatment for AUD may approximately be in the range of 65–70% (Miller et al., 2001). Relapse into drinking in AUD may have different causes. For example, neurobiological predictors for treatment outcome may be abnormal functioning in frontal–striatal circuits (Durazzo et al., 2008; Heinz et al., 2009) or reduced dopamine D2 receptor (DRD2) function as assessed by neuroendocrine methods (Schmidt et al., 1996). Other risk factors for relapse are poor coping skills, low self-esteem, low self-efficacy, social isolation, personality disorders, depression and a greater severity of drinking history (Miller et al., 2003; Bradizza et al., 2006; Moos and Moos, 2006; Walter et al., 2006). However, it is most likely that relapse is caused by a combination of biological, neurocognitive, psychological, psychiatric and socio-demographic factors (for review, see Bradizza et al., 2006).

Even though psychological, socio-demographic and alcohol-related factors thus can predict relapse, there is still a large proportion of the variance that remains unexplained (McKay et al., 2006). Additional explanations may be neurobiological/genetic factors, among them an impairment of the dopaminergic neurotransmission (McKay et al., 2006). Thus, the DRD2 gene, and in particular the TaqIA polymorphism (rs1800497) of this gene, has been extensively studied in relation to alcohol dependence (Noble, 2003). The TaqIA polymorphism has actually been found to be located 10 kb downstream of the DRD2 gene within a protein-encoding region of a neighboring gene, i.e. ankryin repeat and kinase domain containing 1 (Neville et al., 2004). This polymorphism may therefore best be addressed as the TaqIA polymorphism of the DRD2 gene region. It should, however, be noted that this polymorphism is of functional significance since the A1 allele is associated with reduced density and binding of DRD2 (Noble, 2003). The A1 allele has thus been found to be associated with alcohol-dependence and particularly severe forms of this disorder (Noble, 2003; Berggren et al., 2006). Three recent meta-analyses (Mufano et al., 2007; Smith et al., 2008; Le Foll et al., 2009) and an individual study of ours (Berggren et al., 2006), the latter comprising a large number of subjects (total sample: about 1200), have shown an association between the A1 allele and alcohol-dependence, although its effect size is small with an odds ratio (OR) being in the range of 1.2–1.4. In addition, when three single nucleotide polymorphisms in the DRD2 gene were investigated in Indian male alcohol-dependent individuals, a haplotype including the -141C Ins/Del and TaqIA alleles appeared to confer to about 2.5 times greater risk to develop alcohol dependence (Prasad et al., 2010).

In a follow-up (Berggren et al., 2010) of the earlier study of ours (Berggren et al., 2006), we also found that the TaqIA A1 allele is associated with an increased mortality rate during the 10 years follow-up period. Consequently, one question that arises is whether this high mortality rate might be explained by increased relapse proneness, in turn related to the presence of the A1 allele. This prompted us in the present study to investigate whether the TaqIA A1 allele of the DRD2 gene region may be associated with an increased relapse rate in alcohol-dependent individuals. To evaluate influences of other known risk factors for relapse,
psychological and socio-demographic factors were also included and investigated.

MATERIALS AND METHODS

This study is part of an ongoing longitudinal project [Gothenburg Alcohol Research Project (GARP); Berglund et al., 2008; Berglund, 2009]. The aim of GARP is to investigate psychological/psychiatric and neurobiological/genetic characteristics in alcohol-dependent individuals and to evaluate whether these variables influence treatment outcome.

Subjects

For this part of the project, adult women and men with diagnoses of alcohol-dependence (women: n = 10; men: n = 40) were recruited from two Swedish 12-step treatment units for alcoholism with abstinence-oriented treatment programs. The inclusion criteria were that the individuals had to meet the DSM-IV criteria for alcohol-dependence (APA, 1994) and agreed to provide blood for genotyping. The exclusion criterion was that they should be without severe on-going physical and psychiatric disorders other than alcohol- and nicotine-dependence.

The present study was approved by the Ethics Committee of the University of Gothenburg, Sweden. Informed consent was obtained from all participants in the study.

Procedure and instruments

Subjects participating in this study were administered a number of psychological self-rating scales when starting their treatment program. Craving for alcohol was assessed by the Obsessive Compulsive Drinking Scale (OCDS; Anton et al., 1996), self-efficacy with the Alcohol Abstinence Self-efficacy Scale (AASE; DiClemente et al., 1994), and mental health with the Symptom Checklist-90 (SCL-90; Derogatis et al., 1973). Subjective stress levels were assessed by the Perceived Stress Scale (PSS; Cohen et al., 1983) and for personality traits, the Temperament and Character Inventory (TCI; Cloninger et al., 1994) was used.

Subjects were interviewed by a trained interviewer from the research group shortly after the start of treatment. The Addiction Severity Index (ASI) was used as an interview-instrument (McLellan et al., 1992). The ASI items that were used in this study were the socio-demographic (e.g. age, gender, school education and employment) and alcohol-related items (e.g. age at first drinking, grams of pure alcohol per week during the last year, number of years of excessive alcohol intake). On average, 1½ year after the end of the treatment program, subjects were re-interviewed by using the alcohol-related items from the ASI follow-up version. At this interview, subjects self-reported whether they had been drinking alcohol at any time point or had been totally abstinent after the end of treatment. Depending on their post-treatment drinking history, they were then defined as abstainers (no drinking at all during the follow-up period) or relapers (any drinking). The same definition can be seen in other studies—for example, Flannery et al. (1999) and Strowig (2000).

Genotyping

The TaqIA polymorphism (rs1800497) of the DRD2 gene was analyzed using the TaqMan® Allelic Discrimination technology. A Custom TaqMan® SNP Genotyping Assay (Applied Biosystems, Foster City, CA) was designed using the FileBuilder® software (Applied Biosystems). A post-amplification plate read for allelic discrimination was performed in an ABI 7900HT sequence detection instrument (Applied Biosystems) using the SDS® v1.0.1 software supplied with the instrument. Analyses were performed by a certified and experienced laboratory technician at an accredited unit for genetic analyses at the clinical chemistry laboratory of Sahlgrenska University Hospital. Six sequenced internal control samples representative of each genotype (two samples per genotype) and six negative control samples (H2O) were analyzed per 96-well plate. The individual genotype distributions did not deviate significantly from Hardy–Weinberg equilibrium. The call rate was 100% for both TaqMan genotyping and sequencing.

Statistical analyses

For statistical analyses, independent t-test or χ² test (Fisches exact probability test) was used when appropriate. Effect sizes were calculated by Cramér (1999) and Cohen (1988). Significance level of P < 0.05 was used.

RESULTS

Thirty-three (66%) subjects reported that they had relapsed, and 17 (34%) were abstinent during the follow-up period. Socio-demographic and alcohol-related data for the two groups (i.e. relapers and abstainers) are shown in Table 1. Of all the socio-demographic variables, only the total number of DSM-IV criteria for alcohol-dependence differed between the groups. Thus, relapers fulfilled fewer of those criteria than abstainers (5.5 ± 1.4 and 6.3 ± 0.9, respectively; t = 2.11; P < 0.05, effect size: 0.7).

There were no differences between relapers and abstainers in the psychological self-rating scales measuring self-efficacy, mental health, stress, personality or craving (see Table 2).

Thirty-six percent (18/50) of the subjects were carriers of the A1 allele of the DRD2 gene region (i.e. genotypes A1/A1 or A1/A2; A1+ group) and consequently 64% (32/50) non-carriers (i.e. genotype A2/A2; A1− group). There was a difference in relapse rate between carriers of the A1 allele compared with non-carriers with 89% (16/18) relapers in the A1+ group and 53% (17/32) relapers in the A1− group, X² = 6.57; P = 0.01 (see Table 3). OR was 7.1 and the effect size was 0.4.

Time to relapse after the end of treatment was 4.2 ± 3.5 months for the A1+ and 6.3 ± 4.7 for the A1− group (P = 0.25, non significant). Days of heavy drinking during the last 30 days prior to the follow-up interview were 3.7 ± 6.2 (for the A1+ group) and 1.5 ± 2.4 (P = 0.12, non significant) (for the A1− group).

DISCUSSION

The present study is, to our knowledge, the first report of an association between the TaqIA A1 allele of the DRD2 gene.
Table 1. Comparisons between abstainers and relapsers in relation to demographic and alcohol-related characteristics assessed at the start of treatment

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 50)</th>
<th>Abstainers (n = 17)</th>
<th>Relapsers (n = 33)</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>50 ± 9</td>
<td>49 ± 11</td>
<td>50 ± 9</td>
<td>0.72</td>
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<tr>
<td>Male (%)</td>
<td>80</td>
<td>82</td>
<td>78</td>
<td>1.00</td>
</tr>
<tr>
<td>Cohabitant (%)</td>
<td>46</td>
<td>52</td>
<td>42</td>
<td>0.56</td>
</tr>
<tr>
<td>Employed (%)</td>
<td>90</td>
<td>94</td>
<td>88</td>
<td>0.43</td>
</tr>
<tr>
<td>Years of higher education</td>
<td>0.6 ± 1.5</td>
<td>0.8 ± 1.8</td>
<td>0.6 ± 1.3</td>
<td>0.57</td>
</tr>
<tr>
<td>Tobacco use (%)</td>
<td>87</td>
<td>82</td>
<td>90</td>
<td>0.65</td>
</tr>
</tbody>
</table>

Alcohol variables

<p>| | | | | |</p>
<table>
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<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first drinking</td>
<td>15 ± 3</td>
<td>15 ± 3</td>
<td>15 ± 3</td>
<td>0.54</td>
</tr>
<tr>
<td>Age at the onset when using alcohol regularly, (minute three times/week)</td>
<td>32 ± 13</td>
<td>30 ± 14</td>
<td>33 ± 12</td>
<td>0.41</td>
</tr>
<tr>
<td>Age at the onset when regularly intoxicated, (minute two times/week)</td>
<td>33 ± 13</td>
<td>30 ± 15</td>
<td>34 ± 11</td>
<td>0.28</td>
</tr>
<tr>
<td>Years of excessive alcohol intake</td>
<td>13 ± 9</td>
<td>15 ± 10</td>
<td>12 ± 9</td>
<td>0.27</td>
</tr>
<tr>
<td>Alcohol intake during the past year before start of treatment (grams of pure alcohol/week)</td>
<td>909 ± 646</td>
<td>1006 ± 537</td>
<td>865 ± 694</td>
<td>0.50</td>
</tr>
<tr>
<td>No. of drinking days past month before start of treatment</td>
<td>6 ± 9</td>
<td>5 ± 8</td>
<td>7 ± 9</td>
<td>0.14</td>
</tr>
<tr>
<td>No. of previous treatments</td>
<td>2 ± 3</td>
<td>2 ± 4</td>
<td>1 ± 2</td>
<td>0.64</td>
</tr>
<tr>
<td>No. of criteria for alcohol-dependence (DSM-IV)</td>
<td>6 ± 1</td>
<td>6 ± 1</td>
<td>5 ± 1</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or %. Values given in bold indicate statistically significant differences.

Table 2. Comparison between abstainers and relapsers in relation to psychological self-rating scales at start of treatment

<table>
<thead>
<tr>
<th>Scale and subscales</th>
<th>Total (n = 50)</th>
<th>Abstainers (n = 17)</th>
<th>Relapsers (n = 33)</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-efficacy (AASE)</td>
<td>56 ± 18</td>
<td>57 ± 20</td>
<td>56 ± 17</td>
<td>0.80</td>
</tr>
<tr>
<td>Mental health (SCL-90)</td>
<td>72 ± 2</td>
<td>70 ± 18</td>
<td>73 ± 23.3</td>
<td>0.65</td>
</tr>
<tr>
<td>Perceived stress (PSS)</td>
<td>23 ± 11</td>
<td>21 ± 9</td>
<td>24 ± 11</td>
<td>0.32</td>
</tr>
<tr>
<td>Craving (OCDS)</td>
<td>26 ± 10</td>
<td>27 ± 9</td>
<td>25 ± 11</td>
<td>0.53</td>
</tr>
<tr>
<td>Obsessive</td>
<td>9 ± 5</td>
<td>9 ± 5</td>
<td>8 ± 5</td>
<td>0.53</td>
</tr>
<tr>
<td>Compulsive</td>
<td>17 ± 6</td>
<td>18 ± 5</td>
<td>17 ± 6</td>
<td>0.60</td>
</tr>
<tr>
<td>Personality (TCI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novelty Seeking</td>
<td>57 ± 8</td>
<td>58 ± 10</td>
<td>56 ± 8</td>
<td>0.54</td>
</tr>
<tr>
<td>Harm avoidance</td>
<td>54 ± 12</td>
<td>54 ± 11</td>
<td>55 ± 12</td>
<td>0.84</td>
</tr>
<tr>
<td>Reward dependence</td>
<td>50 ± 10</td>
<td>50 ± 8</td>
<td>50 ± 11</td>
<td>0.84</td>
</tr>
<tr>
<td>Persistence</td>
<td>50 ± 11</td>
<td>48 ± 10</td>
<td>50 ± 11</td>
<td>0.56</td>
</tr>
<tr>
<td>Self-directedness</td>
<td>44 ± 12</td>
<td>44 ± 10</td>
<td>44 ± 13</td>
<td>0.98</td>
</tr>
<tr>
<td>Cooperativeness</td>
<td>49 ± 10</td>
<td>51 ± 8</td>
<td>49 ± 11</td>
<td>0.50</td>
</tr>
<tr>
<td>Self-transcendence</td>
<td>51 ± 11</td>
<td>51 ± 9</td>
<td>51 ± 12</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or %.

DRD2 and Relapse in Alcoholism

Table 3. Genotype frequencies (%) according to outcome status

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Abstainers (n = 17)</th>
<th>Relapsers (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1+</td>
<td>2 (11%)**</td>
<td>16 (89%)</td>
</tr>
<tr>
<td>A1−</td>
<td>15 (47%)</td>
<td>17 (53%)</td>
</tr>
</tbody>
</table>

A1+ denotes genotypes A1/A1 or A1/A2 and A1− genotype A2/A2. **P = 0.01 (Fischers exact probability test).

There are some limitations with the present study. First, and probably the most important limitation is that the number of subjects is relatively small and that calculations of ORs in samples of small size can be high by chance. This is

region and a substantially increased self-reported relapse rate at a follow-up of 1½ year after the end of a 12-step treatment program. Although the validity of self-reports may be questioned several studies have shown that self-reports obtained from alcohol-dependent individuals are valid and reliable in follow-up interviews up to 5 years. It has been suggested that this is particularly true in abstinence-oriented treatment program, as is the case of the 12-steps program (for references, see Mann et al., 2005). The overall relapse rate in the present group of subjects was 66 percentage (33 of 50 subjects), which is within the range of 65–70 percentage reported in earlier studies of various treatments for alcohol-dependence (Miller et al., 2001). The relapse rate in the subjects who were carriers of the A1 allele (i.e. genotypes A1/A1 and A1/A2) was 89 percentage (16/18), whereas it was 53 percentage (17/32) in the non-carriers (i.e. genotype A2/A2). This difference was statistically significant, and the OR for relapse in the A1 carriers was high (7.1). The effect size was 0.4 (Cramér V), which should be interpreted as a relatively strong association (Rea and Parker, 1992). Although the number of subjects in the present study was relatively small (n = 50), this obtained OR may nevertheless argues in favor of an association. The reason for the increased relapse rate in the carriers of the A1 allele remains, however, to be elucidated. It should, in this context, be noted that alcohol-dependent subjects who are carriers of the A1 allele have a diminished drinking refusal self-efficacy (Connor et al., 2008). In addition, healthy individuals who are carriers of the A1 allele show impairment in reversal learning situations (Jochem et al., 2009). These two latter studies suggest that alcohol-dependent individuals who are carriers of the A1 allele can benefit from more intense psychological treatment, aimed to improve drinking refusal self-efficacy and relearning to focus on maintenance of abstinence. The importance of improving the treatment of the alcohol-dependent subjects, who are carriers of the A1 allele, is seriously underscored by the finding of highly increased mortality rate in those subjects (Berggren et al., 2010). Furthermore, since the A1 allele is associated with a reduced density of DRD2 (Noble, 2003), the present finding gives additional support to the finding in neuroendocrine studies (see Schmidt et al., 1996) that reduced DRD2 function may be implicated in relapse-proneness in alcohol-dependent individuals.

It was somewhat surprising that there was no influence of psychological or socio-demographic variables on the relapse rate in the present study. This may be explained by the low number of subjects and/or that subjects were recruited from a Swedish 12-step program. Subjects included in this type of treatment should have no severe psychiatric co-morbidity and are usually socially stable, i.e. have an occupation and a permanent residence. This probably hampers the possibility to evaluate the influence of psychological and/or socio-demographic variables on the relapse rate. Moreover, it is also surprising that the relapers fulfilled fewer DSM-IV criteria for alcohol-dependence than abstainers (5.5 versus 6.3 criteria) at the start of the study. The clinical relevance of this small, although significant difference is, however, questionable.

There are some limitations with the present study. First, and probably the most important limitation is that the number of subjects is relatively small and that calculations of ORs in samples of small size can be high by chance. This is
emphasized by characterizing this investigation as a pilot study. Second, only one genetic polymorphism (the Taq 1A) in the DRD2 gene region was investigated. It would be valuable to investigate other genetic polymorphisms of the DRD2 gene and their possible association to relapse. The present finding could therefore serve as an impetus for future studies to include other polymorphisms of the DRD2 gene region.

The finding of the present study thus suggests an association between genotype for the DRD2 and alcohol treatment outcome. Noteworthy, some recent studies have shown a relationship between other genotypes (genetic polymorphisms) and alcohol treatment outcomes. Thus, Wojnar et al. (2006) reported an excess of a specific genotype of the HTR1A serotonin receptor gene and later relapse. In another study comprising 812 alcohol-dependent individuals, carriers of a specific genotype of GABA Aα2 subunit had an improved treatment outcome in a 12-step treatment program (Bauer et al., 2007). Pinto et al. (2008) found that the presence of the short allele of the serotonin transporter promoter polymorphism increased the relapse rate. Moreover, Wojnar et al. (2009) found an association between Val66Met brain-derived neurotrophic factor gene polymorphism and relapse in alcohol-dependence. Finally, Kiefer et al. (2010) recently found that genetic variations in atrial natriuretic peptide transcription factor GATA4 might influence relapse and treatment response to acamprosate.

The findings in these studies and in the present one may therefore encourage future studies to also include genetic polymorphisms of various neurotransmitter systems and evaluate their effects on relapse rates.

Acknowledgements — The authors express their gratitude to research nurse Kathleen Wadell and laboratory technician Mona Seibt Palmér for skilled technical assistance.

Funding — The present study was supported by grants from the Swedish Labour Market Insurance (AFA) and LUA/ALF grants from the Sahlgrenska University Hospital, Gothenburg, Sweden.

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