Genetic Alcohol Sensitivity Regulated by ALDH2 and ADH1B Polymorphisms as Indicator of Mental Disorders in Japanese Employees

Kouichi Yoshimasu1,*, Kanae Mure2, Marowa Hashimoto2, Shigeki Takemura1, Kanami Tsuno1, Mariko Hayashida3, Kenji Kinoshita1, Tatsuya Takeshita2 and Kazuhiisa Miyashita1

1Department of Hygiene, School of Medicine, Wakayama Medical University, Wakayama, Japan, 2Department of Public Health, School of Medicine, Wakayama Medical University, Wakayama, Japan and 3Department of Pharmacy, School of Pharmacy and Pharmaceutical Sciences, Mukogawa Women’s University, Nishinomiya, Japan

*Corresponding author: Department of Hygiene, School of Medicine, Wakayama Medical University, 811-1 Kiiimidera, Wakayama 641-0012, Japan. Tel.: +81-73-441-0646; Fax: +81-73-441-0646; E-mail: kyoshi@wakayama-med.ac.jp

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Abstract — Aims: Alcohol-related disorders (ARD) have been shown to be accompanied by a variety of other comorbid mental disorders. This study evaluated the associations between a variety of mental disorders and genetic alcohol sensitivity. Methods: A total of 1944 Japanese workers were interviewed regarding their mental disorders by the Mini-International Neuropsychiatric Interview (M.I.N.I.). We investigated the relationship of ADH1B rs1229984 and ALDH2 rs671 polymorphisms’ combination with mental disorder risks. Logistic regression analysis was used to evaluate the associations between those polymorphisms and mental disorders, adjusting for sex, age, and job rank. Results: The degree of alcohol sensitivity was classified into five groups according to the combination of ADH1B and ALDH2 genotypes (Group I–V in order starting from the lowest alcohol sensitivity). Those with ALDH2 *1/*1 and ADH1B *1/*1 or with ALDH2 *1/*1 and ADH1B *1/*2, *2/*2 (low sensitivity) were significantly or nearly significantly associated with an increased risk of ARD compared with those with ALDH2 *1/*1 and ADH1B *1/*1 as a reference. Those with ALDH2 *1/*2 and ADH1B *1/*1 were also likely to be at an increased risk of any mental disorder except ARD, as well as disorders without comorbid ARD. This tendency was more apparent among women (OR 11.94, 95% CI 7.03–19.56) and non-drinkers (OR 5.43, 95% CI 1.05–28.23). Conclusion: The genotype combination of ALDH2 *1/*1 and ADH1B *1/*1 is significantly associated with an increased risk of any mental disorder, especially ARD. Non-drinkers or women with ALDH2 *1/*1 and ADH1B *1/*1 are likely to suffer from any mental disorder except ARD.

INTRODUCTION

Alcohol-related disorders (alcohol dependence/abuse, ARD) have been shown to be a critical cause of depression or suicide (Schneider, 2009; Beghi et al., 2013). Given that ARDs are accompanied by a variety of comorbid psychiatric disorders such as bipolar, anxiety, eating and psychotic disorders (Suzuki et al., 2011; Farren et al., 2012; Levy-Ran et al., 2012; Charriau et al., 2013), and that ARD are among the most prevalent psychiatric disorders (Levy-Ran et al., 2012), alcohol sensitivity may affect not only ARD but also a broad range of psychiatric disorders. Though ARD occurs on the basis of psychological vulnerability, moderate alcohol consumption has been shown to be effective for psychological stress reduction (Peele and Brodsky, 2000; Marchard et al., 2003). Since alcohol consumption generally increases in accordance with increased mental strain, a part of moderate drinkers is considered to be affected with ARD (Keyes et al., 2012).

Thus, heavier drinkers (i.e. those with low alcohol sensitivity) tend to suffer from many alcohol-related problems stemming from ARD, leading to isolation from social support and suffering from mental illness. On the other hand, it has been suggested that drinking might help people cope with mental stress (Eckardt et al., 1998; Moore et al., 2007; Anthenelli, 2012; Watt et al., 2014). However, this method may not work for people who cannot drink because of their high alcohol sensitivity, which, in turn, leads to accumulation of the stress. Thus, there is a possibility that genetic alcohol sensitivity is associated with a broad range of mental disorder risks.

Alcohol metabolism occurs in two major steps: oxidation of alcohol to acetaldehyde by the alcohol dehydrogenase enzymes, and further oxidation of acetaldehyde into acetate by aldehyde dehydrogenase enzymes, ALDH2. Single nucleotide polymorphisms (SNPs) of the two enzymes’ gene loci, ADH1B rs1229984 and ALDH2 rs671 SNPs, which show different alcohol/acetaldehyde oxidizing capabilities among individuals, have been reported to exert significant impacts on alcohol consumption and on the risk for ARD in East Asia populations (Higuchi et al., 1996; Takeshita et al., 1996; Whitefield, 2002; Kim et al., 2008). The ADH1B*2 allele represents a much higher activity of ADH1B than the homozygotes for the ADH1B*1 form, enabling fast alcohol elimination and acetaldehyde accumulation in the blood after drinking (Loson and Li, 1986; Yoshida et al., 1991), increasing alcohol sensitivity, and as a result, reducing the risk for ARD. The ALDH2*2 allele encodes a catalytically inactive subunit (Loson and Li, 1986; Yoshida et al., 1991), which causes alcohol-related adverse physical reactions such as flushing, palpitation, nausea, headache and general discomfort (Matsuo et al., 2006). These adverse reactions in subjects with ALDH2*2, which are due to excessive acetaldehyde accumulation, tend to increase alcohol sensitivity and inhibit drinking, subsequently playing a protective role against ARD.

Thus, both mutant alleles of ADH1B*2 and ALDH2*2 are considered to be protective against ARD, while wild alleles of ADH1B*1 and ALDH2*1 have been shown to promote ARD among drinkers (Kim et al., 2008). More concretely, those with the combination of wild homozygote alleles of the two enzymes’ gene loci, ALDH2*1/*1 and ADH1B*1/*1, are expected to be at the greatest risk for ARD. On the other hand, those who have the combination of mutant homozygote alleles of both loci, ALDH2*2/*2 and ADH1B*2/*2, are considered to be least likely to contract ARD. For the sake of clinical convenience, degrees of alcohol sensitivity regulated by the two enzymes’ gene loci can be classified into the following five groups in order of lowest alcohol sensitivity: Group I (ALDH2 *1/*1 and ADH1B *1/*1), Group II (ALDH2 *1/*1 and ADH1B *1/*2, *2/*2), Group III (ALDH2 *1/*2 and ADH1B
Although a few studies have been conducted to determine the combined genetic effect of ALDH2 and ADH1B on ARD (Kim et al., 2008; Yao et al., 2011), there is almost no evidence regarding the combined effect of these two loci on other mental disorders (Hishimoto et al., 2010). The purpose of the current study is to investigate whether subjects with high alcohol sensitivity have low rates of ARD in the Japanese working population, and to clarify the associations between genetic alcohol sensitivity regulated by ALDH2 and ADH1B and a broad range of mental disorders, with explicit assessment of the effects of comorbid ARD as well as gender differences and drinking habit.

METHOD

Participants

Our subjects were 2442 local government employees in the Kinki area of Japan who underwent annual health checkups from May to July 2013. Their work included a variety of clerical jobs, along with jobs in monitoring, security and communication service. The investigators encouraged all employees to enroll in the study; 1944 of whom (79.6%) agreed to participate in an interview survey regarding mental disorders, and provided blood samples to determine the two enzyme genetic polymorphisms. All participants gave written consent. This study was approved by the institutional review board for genetic research of Wakayama Medical University (acceptance number 106).

Psychiatric Structured Interview

The Mini-International Neuropsychiatric Interview (M.I.N.I.), Japanese version 5.0.0 (2003) (Sheehan et al., 1998; Sheehan and Lecrubier, 2003), a conveniently structured tool designed to identify cases of mental disorder, was used for the present screening interview. The reliability and validity of the Japanese version of the M.I.N.I. were reported to be satisfactory (Otsubo et al., 2005), by comparison between M.I.N.I. and Structured Clinical Interview for DSM-III-R as well as by interrater and test-retest reliabilities. A total of 14 interviewers, all of whom were licensed doctors or nurses, were enrolled as competent to conduct the interviews. The first author (K.Y.), a psychiatrist, trained them in essential interview skills, including didactic sessions of the general interview, and reviews of the instrument sections. Furthermore, the first author checked the interviewers and corrected them as the need arose during interview sessions so that the interview could be conducted appropriately.

The M.I.N.I. deals with 17 Axis I mental disorders based on the standard of a 12-month prevalence of 0.5% or more (Sheehan et al., 1998), among which we checked the disorders listed in the first screening session: major depressive disorder, dysthymia, suicidality, manic episode, panic disorder, agoraphobia, social phobia, specific phobia, obsessive-compulsive disorder, general anxiety disorder, ARD, substance dependence/abuse, anorexia nervosa, anorexia bulimia and post-traumatic stress disorders (PTSD), were classified as candidate disorders potentially associated with genetic alcohol sensitivity. These disorders are all included in the M.I.N.I., except psychotic disorders and anti-social personality disorder. All subjects were asked the screening questions essential for the diagnosis of these disorders. If their mental symptoms satisfied those questions, more detailed questions were used to arrive at a final diagnosis of each disorder.

Statistical analysis

The P-value for Hardy–Weinberg equilibrium (HWE) was calculated as the difference between the number of genotypes and the number of alleles (df = 1). As mentioned above, the interview procedure of M.I.N.I. consists of two steps, i.e. a screening step for any mental disorders, and a detailed interview procedure of M.I.N.I. consists of two steps, i.e. a screening step for any mental disorders, and a detailed interview for each disorder found in the screening step. If the subjects answered ‘yes’ to any screening questionnaire, they were regarded as having a ‘preliminary’ diagnosis. Final diagnoses were given if the subjects met the final diagnostic criteria of each disorder. Four models were created for examining the associations between mental disorders and the two enzyme genetic polymorphisms based on the definition of outcome variables (Fig. 1). These outcomes were: (a) alcohol-related disorders, (b) any mental disorders except alcohol-related disorders, (c) any mental disorders without comorbid alcohol-related disorders and (d) any preliminary and final diagnoses of mental disorders. Those who did not correspond to any screening questions except ARD were categorized as normal controls (n = 1437). The screening question for ARD, ‘In the past 12 months, have you had three or more alcoholic drinks within a three-hour period on three or more occasions?’, was used as a proxy for a drinking habit. ‘Three or more alcoholic drinks’ in the Japanese version means three or more glasses (three or more units on average) of any alcoholic beverage. The Japanese ‘standard drink’ of alcoholic is 25 ml, which is 2.5 times that of the UK standard. A detailed interview was conducted on those who answered ‘yes’ to this screening question (i.e. drinkers) to confirm ARD defined by DSM-IV and ICD-10. The detailed interview consisted of seven questions for alcohol dependence and four questions for alcohol abuse. Alcohol abuse was confirmed when the subjects did not meet the criteria for alcohol dependence.

Logistic regression analysis was used to obtain odds ratios (ORs) and 95% confidence intervals (CIs). The dependent variables in that analysis were the four outcomes defined above, which were compared with the 1437 controls. Exploratory variables were ALDH2 and ADH1B genotypes classified as mentioned in the Introduction (Group I–V), adjusting for age, sex and job rank. Age was divided into two categories, <40 or 40+, since two peaks of age distribution were observed at the dividing line of 40 years of age. Job rank was also divided into two categories, administrative position or not.
The ORs and their 95% CIs were obtained from the corresponding logistic regression coefficients and their standard errors. Each OR showed how many times subjects with the genotypes were likely to have been affected by mental disorders compared with Group IV. Group IV was set as the reference group since its members were considered better able to control their alcohol-related behaviors compared with the other lower sensitivity groups (Yokoyama et al., 2010). These multivariate analyses were conducted separately for drinkers and non-drinkers, as well as the entire sample. We also estimated trends of the OR in each model in accordance with the number of wild homozygotes in the two loci. Gene-gene interaction was evaluated by likelihood ratio test in the entire sample with males and females combined. P-values (two-sided) <0.05 were considered statistically significant. All computations were performed using the SAS software package, version 9.1.3 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Distributions of mental disorders as well as demographic backgrounds of the subjects are shown in Table 1. Nearly 90% of the subjects were male and a little more than 10% were employed at administrative positions. The prevalence of mental disorders was low since the subjects were generally from a healthy working population. However, 26.1% of them had some signs of mental disorders. The most frequent disorders were ARD (8.6%). There were 68 subjects who suffered from mental disorders except ARD, while 11 of them had ARD. Thus, only 11 subjects (0.6%) had ARD as well as other comorbid psychiatric conditions, and 57 (2.9%) had mental disorders other than ARD alone. Assuming that the proportion of those with Group II was 50% based on our previous survey (Takeshita, 2012), and that the expected OR of any mental disorder except ARD associated with this group was 3.0 with a statistical power of 0.80, the required sample size of affected cases was calculated to be 66, almost equal to the current results.

The distributions of ALDH2 and ADH1B polymorphisms as well as their combined classification (Group I–Group V) separately for men and women as well as entire samples are shown in Table 2. Distributions between men and women were quite similar, and no significant deviation was detected by HWE among the subjects for both ALDH2 and ADH1B in men and women as well as whole sample. Group II was, as expected, most frequent, and the next most frequent group was Group IV. Group III had the fewest members among the five groups. These genotype distributions were consistent with a previous Japanese study (Takeshita, 2012).
Table 3 shows the association between ALDH2 as well as ADH1B polymorphisms according to their classification, and mental disorders separately for men and women. Group I and Group II were marginally significantly or significantly associated with an increased risk of ARD in men. Group I of women shows 25-fold increased risk of ARD while the 95% CI was too wide due to the small sample size. Group V was significantly associated with less than one-tenth of the decreased prevalence of ARD compared with Group IV in men. Group II showed a modest but significant increase in the risk for any mental disorder (including preliminary diagnoses) in men.

The association between the Group I–V polymorphism classification and mental disorders was evaluated separately for drinkers and non-drinkers (Table 4). Although Group I showed non-significant, modest associations with an increased risk of mental disorders defined as the four outcomes among drinkers, the association between Group I and any mental disorders other than ARD was strong (>5-fold increased risk) and significant in non-drinkers. In this analysis of non-drinkers, ‘any mental disorders except alcohol-related disorders’ (model 2) and ‘any mental disorders without comorbid alcohol-related disorders’ (model 3) had the same outcomes, yielding the same results.

Trends in associations between mental disorders and the two enzyme polymorphisms according to the number of the high-risk genotypes in the two loci (0, 1, and 2) are shown in Table 5. Significant trends were observed for ARD and any mental disorders including preliminary diagnoses, whereas trends for ‘any mental disorders except alcohol-related disorders’ (model 2) and ‘any mental disorders without comorbid alcohol-related disorders’ (model 3) were far from statistically significant. When those analyses were conducted separately for drinkers and non-drinkers, calculated statistics were far from significant (data not shown), except for a non-significant modest trend for any mental disorders including preliminary diagnosis (P = 0.096) among drinkers. Gene-gene interactions between ALDH2 and ADH1B on mental disorders were not statistically significant (P = 0.36 for ‘any mental disorders except alcohol-related disorders’, 0.32 for ‘any mental disorders without comorbid alcohol-related disorders’, 0.37 for any mental disorders including preliminary diagnoses, and 0.16 for ARD).

**DISCUSSION**

Individual alcohol sensitivity is strongly regulated by the combination of ALDH2 and ADH1B genotypes. The current study first applied the classification of the combined effects of the two alcohol metabolizing enzymes’ polymorphisms (i.e. Group I–V) to the prevalence of various kinds of mental disorders. Compared with Group IV (ALDH2 *1/*1 and ADH1B *1/*1) and Group II (ALDH2 *1/*2 and ADH1B *1/*1), who are considered to have self-inhibition against alcohol-related behaviors, Group I (ALDH2 *1/*1 and ADH1B *1/*2) and Group V (ALDH2 *2/*2 and ADH1B *1/*1, *1/*2, *2/*2) were at a significantly elevated risk for ARD, especially in women. The genotype combination of Group I also tended to be associated with an increased risk of other mental disorders, as well as such disorders without comorbid ARD, while there were no material associations between Group II and those disorders. Such associations of Group I and mental disorders except or without ARD were more apparent in women and non-drinkers. In addition, many of the high-risk genotypes in the two loci (alleles related to low alcohol sensitivity) were significantly associated with ARD and any mental disorders, including preliminary diagnoses.

These findings suggest that those with low alcohol sensitivity are more likely to be affected with ARD than those with high alcohol sensitivity, consistent with previous findings (Kim et al., 2008; Yokoyama et al., 2010; Yao et al., 2011). The observed strong associations between Group I and ARD as well as other mental disorders in women should be interpreted with caution because few women had such mental disorders, leading to non-significant findings. Female alcohol-dependents have been shown to be more likely to have psychiatric comorbidities than male alcohol-dependents (Higuchi et al., 1993; Grant and Harford, 1995; Kessler et al., 1997), consistent with the current findings. On the other hand, effects of ALDH2 and ADH1B were reported to differ between men and women; female alcohol-dependents with ALDH2*2 were shown to develop ARD earlier than those with ALDH2*1,
resulting in having other psychiatric comorbidities (Kimura et al., 2011). Since subjects of this study were hospitalized patients, it might be difficult to apply their results to the general working population.

The strong associations between Group I or Group II and ARD may be among the causes that explain the positive associations between those genotype combinations and overall mental disorders (model 4). On the other hand, those with $ADH1B^{*1/*1}$ and $ADH1B^{*1/*2}$ were at an elevated risk for mental disorders except or without ARD, while Group II and Group III were not. Unexpectedly, this tendency was more apparent among women or those without actual drinking habits.

Non-drinkers in Group I were confronted by a more than 5-fold increased risk of mental disorders except ARD, compared with those of Group IV.

Thus, although those with low alcohol sensitivity tended to be affected with ARD, their other mental problems, especially for those with very low sensitivity (Group I), seem not to come directly from ARD or its related behavioral and psychosocial adversities. The reason why Group I was strongly associated with mental disorders excluding ARD among non-drinkers is unclear. One possible explanation is that it is beneficial to drink alcohol for those with very low alcohol sensitivity to alleviate undesired emotional states. Such behavioral effects of moderate

| Table 3. Associations between $ALDH2$ and $ADH1B$ polymorphisms and mental disorders among men and women |
|-----------------------------------|---------------|---------------|---------------|---------------|
| Groups | Model 1<sup>a</sup> | Model 2<sup>b</sup> | Model 3<sup>c</sup> | Model 4<sup>d</sup> |
|        | OR     | 95% CI | OR     | 95% CI | OR     | 95% CI | OR     | 95% CI |
| Men | (n = 1742) | | | | | | | |
| Group I | 2.51 | 0.91–6.92 | 2.34 | 0.66–8.31 | 2.51 | 0.70–8.96 | 1.46 | 0.72–2.96 |
| Group II | 2.27 | 1.55–3.32 | 0.88 | 0.50–1.55 | 0.73 | 0.39–1.37 | 1.32 | 1.05–1.67 |
| Group III | 2.43 | 0.88–6.67 | 0.73 | 0.10–5.58 | 0.81 | 0.11–6.23 | 1.52 | 0.77–3.00 |
| Group IV | 1.00 | ref | 1.00 | ref | 1.00 | ref | 1.00 | ref |
| Group V | 0.09 | 0.01–0.69 | 0.46 | 0.14–1.56 | 0.51 | 0.15–1.74 | 0.80 | 0.52–1.22 |
| Women | (n = 202) | | | | | | | |
| Group I | 26.29 | 1.14–608.06 | 7.86 | 0.54–114.33 | 11.94 | 0.73–195.63 | 4.08 | 0.71–23.34 |
| Group II | 3.18 | 0.35–29.28 | 1.34 | 0.31–5.85 | 2.00 | 0.37–10.72 | 1.42 | 0.70–2.86 |
| Group III | NA | NA | NA | NA | NA | NA | NA | NA |
| Group IV | 1.00 | ref | 1.00 | ref | 1.00 | ref | 1.00 | ref |
| Group V | NA | NA | 1.63 | 0.15–17.23 | 2.42 | 0.20–29.19 | 0.56 | 0.12–2.76 |

Adjusted for age and job rank in each model. Controls are 1285 for men and 202 for women without any preliminary or final psychiatric diagnoses in all four models. NA = not available due to lack of subjects within the categories. Group I ($ALDH2^{*1/*1}$ and $ADH1B^{*1/*1}$); Group II ($ALDH2^{*1/*1}$ and $ADH1B^{*1/*2,*2/*2}$); Group III ($ALDH2^{*1/*2}$ and $ADH1B^{*1/*1}$); Group IV ($ALDH2^{*1/*2}$ and $ADH1B^{*1/*2,*2/*2}$); Group V ($ALDH2^{*2/*2}$ and $ADH1B^{*1/*1,*1/*2,*2/*2}$). Any mental disorders except alcohol-related disorders, $n = 1447$ for men and 158 for women. Any mental disorders except or without ARD, while Group II and Group III were not. Unexpectedly, this tendency was more apparent among women or those without actual drinking habits.

Table 4. Associations between $ALDH2$ and $ADH1B$ polymorphisms and mental disorders among drinkers and non-drinkers

<table>
<thead>
<tr>
<th>Groups</th>
<th>Model 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Model 2&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Model 3&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Model 4&lt;sup&gt;d&lt;/sup&gt;</th>
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<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Drinker</td>
<td>(n = 1149)</td>
<td></td>
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<tr>
<td>Group I</td>
<td>1.95</td>
<td>0.74–5.16</td>
<td>1.68</td>
<td>0.35–7.96</td>
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<tr>
<td>Group II</td>
<td>1.65</td>
<td>1.12–2.43</td>
<td>0.92</td>
<td>0.47–1.79</td>
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<tr>
<td>Group III</td>
<td>1.87</td>
<td>0.66–5.34</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Group IV</td>
<td>1.00</td>
<td>ref</td>
<td>1.00</td>
<td>ref</td>
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<tr>
<td>Group V</td>
<td>0.45</td>
<td>0.06–3.51</td>
<td>NA</td>
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</tbody>
</table>

Non-drinkers in Group I were confronted by a more than 5-fold increased risk of mental disorders except ARD, compared with those of Group IV.

Thus, although those with low alcohol sensitivity tended to be affected with ARD, their other mental problems, especially for those with very low sensitivity (Group I), seem not to come directly from ARD or its related behavioral and psychosocial adversities. The reason why Group I was strongly associated with mental disorders excluding ARD among non-drinkers is unclear. One possible explanation is that it is beneficial to drink alcohol for those with very low alcohol sensitivity to alleviate undesired emotional states. Such behavioral effects of moderate
drinking can encompass events that the human or other animal can perceive as reinforcing through either positive (e.g. pleasurable) or negative (e.g. stress reduction) reinforcement mechanisms (Eckardt et al., 1998). However, if they cannot drink for any reason, the accumulated stress is expected to be serious enough to lead them to many kinds of mental disorders.

Another explanation is that Group I members are few among the Japanese, while a majority of the European population (Caucasians) are included in this group (Lorenzo et al., 2006; Kayaalp and Soylemezoglu, 2010). In regions where Group I is popular, where drinking habits are considered relatively uniform, those of Group I can drink heavily without hesitating. However, in Japan, it might be difficult for them to drink as much as they want, given their surroundings. As a reaction to such stress, they might quit drinking and then develop some mental disorders.

Third, impulsivity-related personality traits such as lack of premeditation, lack of perseverance, sensation seeking, negative urgency, positive urgency and reward sensitivity have been generally shown to be associated with alcohol consumption and problematic alcohol use (Stautz and Cooper, 2013). Thus, some specific personality traits linked with Group I may lead to a variety of mental disorders.

Strengths and limitations

The results in this study should be interpreted in the context of their strengths and limitations. Two important methodological strengths are noteworthy. First, this is the first study to investigate the relationships between various kinds of mental disorders with ALDH2 and ADH1B polymorphisms, unlike the majority of previous studies on this issue which focused on ARD only. Second, we studied a large sample of employees who allowed us to conduct statistical analyses in accordance with the combination of the two enzymes’ genotypes (i.e. Group I–V classifications).

On the other hand, three potential limitations are noteworthy. In spite of the large sample size, few subjects were having mental disorders except or without ARD evaluated by the structured interview since our subjects were generally healthy employees, and not those recruited from patients having mental disorders. Although a few of the subjects might have been found to have disorders partially because of the M.I.N.I. that evaluates the point (current) prevalence rather than the 12 months or lifetime prevalence, severity of the mental disorders is not considered to be so grave as to hinder working, which, in turn, is not always representative of the clinical disorders. ARD are also considered not so severe; rather, it might even be somewhat overestimated due to the drinking culture specific to the male-dominant workplace, leading to difficulty in generalizing the findings. However, prevalence of ARD was considered to be relatively accurate compared with the other disorders since it was estimated at 12 months prevalence.

Next, the reason why subjects with ALDH2 *1/*1 and ADH1B *1/*1 among the non-drinkers did not drink was unclear. Several possible interpretations for why they suffered from mental disorders except ARD depended on whether they wanted to drink or not. For those who wanted to drink, some mental disorders arose from the psychological frustration of desiring drinking, as mentioned above. However, if they disliked drinking, the mechanism that explains the associations between Group I and mental disorders except ARD would be difficult to understand and would remain inconclusive. One speculation is that some personality traits leading to mental disorders might be genetically linked with the genotype combination of Group I.

Lastly, as the onset age of mental disorders could not be confirmed by M.I.N.I., it could not be ascertained whether or not ARD preceded the other comorbid mental disorders. In other words, one cannot determine which mental disorder is alcohol-induced or independent. However, it is noteworthy that only 6.5% of the subjects with ARD had comorbid mental disorders.

CONCLUSIONS

The current study demonstrates that alcohol sensitivity regulated by ALDH2 and ADH1B polymorphisms may be a useful indicator of mental disorders. Further larger scale, cross-cultural, clinical or population-based studies undoubtedly will lead to a more thorough understanding of the role of gene polymorphisms related to alcohol metabolism in the development of mental illness.

AUTHORS’ CONTRIBUTIONS

K.Y. is principle investigator and wrote the draft of the manuscript. K.Mu., M.Has., M.Hay. and K.K. conducted genetic analysis. S.T. and K.T. assisted the field survey. T.T. gave the principle investigator special advices in interpreting the findings. K.Mi. superintended the entire study.
Eckardt MJ, File SE, Gessa GL

Keyes KM, Hatzenbuehler ML, Grant BF

Hayashida M, Ota T, Ishii M


