Aldehyde Dehydrogenase 2 and β_3-Adrenergic Receptor Gene Polymorphisms: Their Association With Elevated Liver Enzymes and Metabolic Syndrome

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Recent studies indicate that some patients with nonalcoholic fatty liver have ongoing liver injury that may progress from steatosis to steatohepatitis or fibrosis. The present study was designed to clarify the clinical features of liver dysfunction observed in the course of workplace physical check-ups in relation to multiple risk factor syndrome including obesity, hyperlipidemia, hypertension, and impaired glucose tolerance, and to clarify the involvement of aldehyde dehydrogenase 2 (ALDH2) and β_3-adrenergic receptor (β3-AR) gene polymorphisms in elevation of liver enzymes. One hundred forty-eight male workers 35 years of age were enrolled. They were requested to answer questionnaires about drinking and smoking habits, and underwent urinalysis, physical and peripheral blood examinations, blood chemistry, electrocardiogram and chest x-rays. The genotypes of ALDH2 and β3-AR were analyzed by polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP). The subjects were divided into active ALDH2 or inactive ALDH2 groups. They were also divided into 2 groups according to the β3-AR genotype. The relationships between ALDH2 and β3-AR gene polymorphism and the results of the physical examination including liver function tests were analyzed. The subjects were also divided according to the number of components of metabolic syndrome. The prevalence of elevated alanine aminotransferase (ALT) level increased with the accumulation of components of metabolic syndrome. Active ALDH2 was associated with elevated ALT level to a greater degree than β3-AR polymorphism. Among those with normal body mass index (BMI), the genotypes of ALDH2 and β3-AR were strongly associated with elevated ALT level. Logistic regression analysis revealed that BMI, triglyceride level, and ALDH2 genotype were associated with ALT elevation. In conclusion, evaluating the genotype of ALDH2 and β3-AR may assist in predicting and preventing the development of fatty liver which may be related to multiple risk factor syndrome.

NONALCOHOLIC fatty liver disease (NAFLD) is the most common form of liver disease in various countries. It is estimated to affect 10% to 24% of the general population.[1] NAFLD has been thought to be a relatively benign disease compared with chronic liver diseases caused by hepatitis B virus (HBV) or hepatitis C virus (HCV). However, a recent study indicated that some patients with nonalcoholic fatty liver have ongoing liver injury that may progress from steatosis to steatohepatitis or fibrosis.[2]

NAFLD is more common among patients with obesity, type 2 diabetes mellitus, and dyslipidemia.[2,3] Although the cause of NAFLD is not known, recent studies showed that most patients with NAFLD have hyperinsulinemia and insulin resistance regardless of the severity of liver inflammation.[4,5] These findings indicate the importance of insulin resistance as a causal role in the development of NAFLD.

Recently we noted that some younger people at one workplace had elevated liver enzyme levels in their routine medical examinations.[6,7] Among those aged 20 to 29 years, an abnormal liver function test was the only frequent finding. Since the majority of these workers were nonhabitual drinkers with no history of habitual drug use, showing negative for HBV, HCV, and markers of autoimmune hepatitis, it appears that they had NAFLD.[8]

Several reports indicate that polymorphism of β_3-adrenergic receptor (β3-AR) is related to insulin resistance or visceral fat obesity.[9-15] Therefore, we were interested in understanding the relationship between β3-AR polymorphism and alanine aminotransferase (ALT) level elevation in the development of fatty liver. Moreover, since chronic alcohol intake and acetaldehyde have been reported to be closely related with insulin resistance[16-18] and 40% of the Japanese population have a polymorphism of the aldehyde dehydrogenase 2 (ALDH2) gene, which plays a major role in the metabolism of ethanol in the liver, ALDH2 polymorphism may be another candidate for elevated liver enzymes. Additionally, we observed that inactive ALDH2 worsens glycemic control in patients with type 2 diabetes mellitus who drink low to moderate amounts of alcohol.[19]

Thus, the present study was designed to investigate the association between the clinical features of workers with elevated activity of liver enzymes and the involvement of the ALDH2 and β3-AR genes in liver dysfunction among young workers.

MATERIALS AND METHODS

Study Subjects

The subjects were 148 employees working at a car sales company in Japan. Since workers are required by law in Japan to have a routine health examination including blood chemistry at 35 years of age, we selected subjects who were 35 years of age who visited the medical clinic in the company between September 1, 1998, and July 31, 1999. Although about 400 workers at the company were 35 years of age during the period of investigation, approximately 50% of the workers

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preferred to go to a hospital for a complete medical examination, while the remaining workers visited the clinic at the company. The 148 workers who visited the clinic at the company during the period in question and who agreed to participate took part in the present study.

The industrial physician explained the purpose of the study to each worker. Each subject was asked to provide information on past medical history of illnesses and to fill out questionnaires regarding drinking and smoking habits, diet, health conditions, physical activity, sleeping time, and current drug use. The subjects underwent a physical examination, conventional laboratory tests including urinalysis, peripheral blood examination (red and white blood cell counts, hemoglobin), clinical chemistry (blood sugar level, total cholesterol, triglyceride, high-density lipoprotein [HDL]-cholesterol, creatinine, aspartate aminotransferase [AST], ALT, γ-glutamyl transpeptidase [γ-GTP]), electrocardiogram, and chest x-rays.

No subject had any health complaints, and no subject was undergoing therapy for hypertension, dyslipidemia, or diabetes mellitus. All subjects agreed to undergo genetic testing of their ALDH2 and β3-AR genes. All subjects signed informed consent forms to participate in this study. The ethics committee of the Tokai University School of Medicine, as well as the health care committee of the company approved the study protocol.

Genotype Analysis of the ALDH2 and β3-AR Genes

Genomic DNA was prepared from leukocytes using QIAamp DNA Blood kit (QIAGEN, Tokyo, Japan), and the genotypes of the ALDH2 and β3-AR genes of all subjects were analyzed. The genotype of the ALDH2 gene was examined by polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP), using the procedure described by Yokoyama et al with the restriction enzyme *Mbo*II.[20] Subjects with the ALDH2*1/*1 genotype were classified as having active ALDH2, and subjects with the ALDH2*1/*2 or ALDH2*2/*2 genotype were classified as having inactive ALDH2, as the ALDH2*1/*2 genotype shows nearly null activity compared to that of the ALDH2*1/*1 genotype.[20]

The β3-AR gene was analyzed for the Trp64Arg polymorphism by PCR-RFLP using the procedure described by Widen et al[14] with the restriction enzyme *Bst*Ol. In most of the statistical analyses, we combined the Arg/Arg and Trp/Arg genotypes because the frequency of the Arg/Arg genotype was low.

Alcohol Drinking and Smoking Habits

The subjects filled out questionnaires about alcohol drinking and smoking habit. To avoid underreporting the amount of alcohol or tobacco and obtain accurate data, we explained to the subjects that the questionnaires would be used only for research purposes.

Regarding drinking habit, the questionnaire asked about the number of drinking days per week and daily alcohol intake. This was classified into 4 groups: none; less than 30 g of alcohol per day; 30 g per day; and more than 30 g per day. The amount of alcohol intake was calculated using the following standards: one 350-mL can of beer, one 120-mL glass of table wine, and one 90-mL cup of Japanese sake each contains 10 g of alcohol.[1]

Questions on smoking included the number of cigarettes per day and smoking history.

Evaluation of Liver Dysfunction

The serum levels of three liver enzymes, ie, AST, ALT, and γ-GTP, were used to determine liver dysfunction. A subject was considered to have liver dysfunction if AST was greater than 40 IU/L, ALT greater than 40 IU/L, and/or γ-GTP greater than 60 IU/L.

Table 1. Characteristics of the 148 Male Subjects Who Underwent Routine Physical Examination

	Mean ± SD
Age (yr)	35.2 ± 0.4
Height (cm)	171.3 ± 6.1
Body weight (kg)	69.0 ± 11.1
Body mass index (kg/m^2)	23.5 ± 3.4
Systolic blood pressure (mm Hg)	127.9 ± 13.2
Diastolic blood pressure (mm Hg)	81.1 ± 9.3
AST (IU/L)	23.4 ± 13.4
ALT (IU/L)	28.0 ± 21.4
γ-GTP (IU/L)	30.6 ± 25.5
Fasting plasma glucose (mg/dL)	91.3 ± 8.9
Creatinine (mg/dL)	0.9 ± 0.1
Total cholesterol (mg/dL)	207.7 ± 39.0
HDL-cholesterol (mg/dL)	59.1 ± 11.5
Triglyceride (mg/dL)	118.7 ± 80.7
No. of subjects (%)	
Obesity*	51 (34.5%)
Hypertension†	39 (26.4%)
Dyslipidemia‡	71 (48.0%)
Impaired glucose tolerance§	6 (4.1%)

*If BMI was >24.2, which is 10% higher than the normal BMI.

†If systolic blood pressure was >140mm Hg or diastolic pressure was >90 mm Hg.

‡If total cholesterol level was >220 mg/dL or triglyceride level was >150 mg/dL.

§If fasting plasma glucose level was >110 mg/dL.

Evaluation of the Components of Metabolic Syndrome

We evaluated the subjects for obesity, hypertension, dyslipidemia, and impaired glucose tolerance as the risk factors for multiple risk factor syndrome, and the upper and lower limits for the risk factors are shown in parentheses. We categorized the subjects into the following 3 groups according to body mass index (BMI): lean (BMI $<$ 19.8; lower than 10% of normal BMI, 22), normal (19.8 $\leq$ BMI $<$ 24.2), and obese (24.2 $\geq$ BMI; higher than 10% of normal BMI, 22). Hypertension (systolic blood pressure $\geq$ 140 mm Hg and/or diastolic blood pressure $\geq$ 90 mm Hg), dyslipidemia (total cholesterol level $\geq$ 220 mg/dL and/or triglyceride level $\geq$ 150 mg/dL), and impaired glucose tolerance (fasting plasma glucose level $\geq$ 110 mg/dL) were also measured.

Statistical Analyses

Categorical variables were assessed by the chi-square test or Fisher's exact test. Quantitative values are expressed as the mean ± SD. The significance of differences between groups was analyzed by the Student's unpaired *t* test, Mann-Whitney *U* test, 2-way analysis of variance (ANOVA), and post hoc tests. Logistic regression analysis was performed to predict factors that are associated with an elevated ALT level, and the factors examined were ALDH2 genotype, β3-AR genotype, and laboratory and physical data. A level of $P < .05$ was considered significant. All analyses were performed with the computer program StatView 5.0 (SAS Institute, Cary, NC), except for the logistic regression analysis, which was performed with SPSS 10.0 (SPSS Inc, Tokyo, Japan).

RESULTS

Characteristics of the 148 Male Subjects

The physical and clinical chemistry data of the 148 male subjects are summarized in Table 1. None of the subjects had

Table 2. Comparison of Clinical Data of Subjects Who Did or Did Not Have Liver Dysfunction

	Subjects With Liver Dysfunction	Subjects Without Liver Dysfunction	*P* Value*
No. of subjects	28	120	
BMI (kg/m^2)†	26.4 ± 3.5†	22.8 ± 3.0	<.0001
Systolic blood pressure (mm Hg)	135.0 ± 11.1	126.3 ± 13.1	.0003
Diastolic blood pressure (mm Hg)	87.2 ± 7.9	79.7 ± 9.0	<.0001
Fasting plasma glucose (mg/dL)	92.5 ± 8.8	91.0 ± 8.9	.578
Total cholesterol (mg/dL)	230.0 ± 42.1	202.5 ± 36.5	.0030
Triglyceride (mg/dL)	199.8 ± 113.6	99.8 ± 56.7	<.0001
	No. of subjects (%)		
Obesity‡	20 (71.4%)	31 (25.8%)	<.0001
Hypertension§	16 (57.1%)	23 (19.2%)	<.0001
Dyslipidemia¶	23 (82.1%)	48 (40.0%)	<.0001
Impaired glucose tolerance‖	2 (7.1%)	4 (3.3%)	.357

*P values were determined by Mann-Whitney U test (upper table) or chi-square test and Fischer's exact test (lower table).
†Values are mean ± SD
‡If BMI was >24.2, which is 10% higher than the normal BMI.
§If systolic blood pressure was >140 mm Hg or diastolic pressure was >90 mm Hg.
¶If total cholesterol level was >220 mg/dL or triglyceride level was >150 mg/dL.
‖If fasting plasma glucose level was >110 mg/dL.

chronic liver disease caused by HBV or HCV infection. Of the 148 subjects, 28 had liver dysfunction according to the criteria described earlier. They included 8 subjects with elevated AST level (5.4%), 23 with elevated ALT level (15.5%), and 14 with elevated γ-GTP level (9.5%). The subjects with elevated liver enzymes underwent ultrasonography to confirm the fatty infiltration of the liver. Excluding other liver diseases such as autoimmune and drug-induced, and known metabolic disorders by further serological tests, and based on the questionnaire responses regarding drinking habit (<30 g of alcohol per day), the majority of subjects were diagnosed as having nonalcoholic fatty liver. The percentages of subjects who had obesity, hypertension, dyslipidemia, or impaired glucose tolerance were 34.5%, 26.4%, 48.0%, and 4.1%, respectively. There was 1 patient with abnormal liver enzymes who did not have any of the 4 components of metabolic syndrome, ie, hypertension, dyslipidemia, glucose intolerance, and obesity.

Comparison of Clinical Data Between Subjects With or Without Liver Dysfunction

Twenty-eight subjects (18.9%) had liver dysfunction. BMI, blood pressure, total cholesterol level, and triglyceride level of the subjects with liver dysfunction were significantly higher than the respective values among the subjects without liver dysfunction (Table 2). The proportion of subjects with obesity, hypertension, and dyslipidemia was significantly high in the liver dysfunction group (Table 2).

Alcohol Drinking and Smoking Habits

One hundred thirty-four subjects filled out completely the questionnaire regarding drinking habits, and the same number of subjects answered completely the questions regarding smoking (Table 3). There were no significant differences in the level of alcohol consumption per week ($P = .2028$), amount of daily alcohol intake ($P = .7420$), and smoking (never; former; <20 cigarettes per day; >20 cigarettes per day) ($P = .2500$), between those who did and those who did not have liver dysfunction.

Comparison of Liver Function Among the Four Groups Classified According to the Number of Components of Metabolic Syndrome

Forty-nine (33.1%) of the 148 subjects had no component, 49 (33.1%) had one component, 35 (23.6%) had 2 components, 12 (8.1%) had 3 components, and 3 (2.0%) had 4 components of metabolic syndrome (Table 4). Ninety-nine subjects (66.9%) had 1 or more components of metabolic syndrome. The AST, ALT, and γ-GTP levels gradually increased as the number of components of metabolic syndrome increased (AST, $P = .0003$; ALT, $P < .0001$; γ-GTP, $P < .0001$, ANOVA). Subjects with 2 or more components of the metabolic syndrome

Table 3. Comparison of Alcohol Intake and Smoking Habit of Subjects Who Did or Did Not Have Liver Dysfunction

	Subjects With Liver Dysfunction	Subjects Without Liver Dysfunction
Alcohol intake	n = 21	n = 113
Days/week	3.1 ± 2.3	3.9 ± 2.5
Amount/day		
0	4 (19.0%)	17 (15.0%)
<30 g ethanol	9 (42.9%)	46 (40.7%)
=30 g ethanol	4 (19.0%)	34 (30.1%)
>30 g ethanol	4 (19.0%)	16 (14.2%)
Smoking	n = 22	n = 112
Never	8 (36.4%)	36 (32.1%)
Former	4 (18.2%)	7 (6.3%)
Current		
≤20 cigarettes/d	8 (36.4%)	56 (50.0%)
>20 cigarettes/d	2 (0.9%)	13 (11.6%)

Table 4. Accumulation of Risk Factors and The Levels of AST, ALT, and γ-GTP

	No. of Risk Factors				
	0	1	2	≥3	*P* Value
No. of subjects	49	49	35	15	
AST (IU/L)	19.8 ± 4.7	20.4 ± 6.3	30.3 ± 23.4*	28.8 ± 11.0	.0003
ALT (IU/L)	18.3 ± 8.3	22.5 ± 14.5	41.5 ± 28.8†	45.9 ± 24.2‡	<.0001
γ-GTP (IU/L)	17.8 ± 9.3	28.4 ± 20.0	47.5 ± 32.8§	40.5 ± 33.7¶	<.0001

NOTE. Each value represents mean ± SD. Risk factors were defined by obesity, hypertension, dyslipidemia, and impaired glucose tolerance as the components of metabolic syndrome.

*$P = .0038$ *v* subjects without risk factors by Scheffe's test.

†$P < .0001$ *v* subjects without risk factors by Scheffe's test.

‡$P < .0001$ *v* subjects without risk factors by Scheffe's test.

§$P < .0001$ *v* subjects without risk factors by Scheffe's test.

¶$P = .0124$ *v* subjects without risk factors by Scheffe's test.

had higher values on the liver function test than those without risk factors.

Association of Liver Dysfunction With Frequency of ALDH2 and β3-AR Polymorphisms

Table 5 shows the association of liver dysfunction with the ALDH2 and β3-AR genotypes. Active ALDH2 tended to be seen more frequently among those with liver dysfunction than among those who did not have liver dysfunction, although the difference was not significant ($P = .0745$, χ^2 test). No relationship between β3-AR gene polymorphism and liver function was evident among the subjects.

Association of Liver Dysfunction With Frequency of ALDH2 and β3-AR Polymorphisms Among Those With Normal BMI

Subjects with normal BMI ($19.8 \leq BMI < 24.2$) and elevated ALT level (>40) had active ALDH2 and the Arg/Arg or Trp/Arg genotype of β3-AR (Table 6). In the lean and obese BMI groups, there was no correlation between liver dysfunction and prevalence of β3-AR or ALDH2 polymorphism.

Table 5. Prevalence of Genotype of ALDH2 and β3-AR Genes in Subjects with or without Liver Dysfunction

	Subjects With Liver Dysfunction (n = 28)	Subjects Without Liver Dysfunction (n = 120)	
ALDH2 genotype			
ALDH2*1/*1	19 (67.9%)	59 (49.2%)	
ALDH2*1/*2	8 (28.6%)	55 (45.8%)	
ALDH2*2/*2	1 (3.6%)	6 (5.0%)	
ALDH2 activity			
Active (ALDH2*1/*1)	19 (67.9%)	59 (49.2%)	$\chi^2 = 3.18$
Inactive (ALDH2*1/*2 + ALDH2*2/*2)	9 (32.1%)	61 (50.8%)	$P = .075$
β3-AR genotype			
Trp64Trp	17 (60.7%)	85 (70.8%)	
Arg64Trp	11 (39.3%)	28 (23.3%)	
Arg64Arg	0 (0.0%)	7 (5.8%)	
β3-AR allele			
Trp64	45 (80.4%)	198 (82.5%)	$\chi^2 = 0.14$
Arg64	11 (19.6%)	42 (17.5%)	$P = .709$

Association of ALT Level With the ALDH2 and β3-AR Genotypes in the Normal BMI Group ($19.8 \leq BMI < 24.2$)

We analyzed the relationship between ALT level and ALDH2 or β3-AR genotype in the normal BMI group by 2-way ANOVA and post hoc test. The ALT level of the subjects with the Arg/Arg or Trp/Arg genotype of β3-AR was significantly higher than that of the subjects with the Trp/Trp genotype of β3-AR ($P = .0390$, Scheffe's test) (Fig 1). The ALT level of the subjects with active ALDH2 was significantly higher than that of the subjects with inactive ALDH2 ($P = .0286$, Scheffe's test) (Fig 1).

The AST level was significantly higher among those with the Arg/Arg or Arg/Trp genotype of β3-AR than among those with the Trp/Trp genotype (β3-AR, $P = .0257$; ALDH2, $p = .1404$, Scheffe's test), and the γ-GTP level was significantly higher among those with active ALDH2 than among those with inactive ALDH2 (β3-AR, $P = .1556$; ALDH2, $P = .0351$, Scheffe's test).

Logistic Regression Analysis to Predict Factors Associated With Elevated ALT Level

Logistic regression analysis was performed to determine factors that are independently associated with elevated ALT level. Variables included BMI, total cholesterol level, triglyceride level (continuous variables), alcohol and smoking habits, and the ALDH2 and β3-AR genotypes (categorical variables). By forward stepwise variable selection, the BMI, triglyceride level, and active ALDH2 genotype were independently associated with an elevated ALT level (Table 7).

DISCUSSION

The growing epidemic of noncommunicable diseases can be seen not only in developed countries but also in less-developed countries by rapid demographic and lifestyle changes including alcohol drinking habit, high calorie intake, low physical activity, and stress.[21] These changes in lifestyle lead to obesity, hyperlipidemia, hyperglycemia, hypertension, and other metabolic disorders, including NAFLD. It has been suggested that insulin resistance is a basic condition in these systemic metabolic disorders.[22] The subjects with liver dysfunction in the present study had elevated values of BMI, blood pressure, total

Table 6. Relationship Between Elevated ALT and the ALDH2 and β3-AR Genotypes

ALDH2 genotype	Active		Inactive	
β3-AR genotype	Arg64Arg Trp64Arg	Trp64Trp	Arg64Arg Trp64Arg	Trp64Trp
All subjects (n = 148)				
ALT >40 IU/L (n = 23)	6 (26.1%)	9 (39.1%)	3 (13.0%)	5 (21.7%)
ALT ≤40 IU/L (n = 125)	21 (16.8%)	42 (33.6%)	16 (12.8%)	46 (36.8%)
19.8 ≤ BMI < 24.2 (n = 80)				
ALT >40 IU/L (n = 4)	4 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ALT ≤40 IU/L (n = 76)	12 (15.8%)	27 (35.5%)	11 (14.5%)	26 (34.2%)

cholesterol, and triglyceride, which are components of the metabolic or X syndrome, compared with the respective values in the subjects without liver dysfunction (Table 2). As shown in Table 4, AST, ALT, and γ-GTP levels gradually increased as the number of components of metabolic syndrome increased. These results suggest that a finding of liver dysfunction among workers in the course of routine physical examination at the workplace is relevant to metabolic syndrome.

One of the limitations of our study is the lack of histological confirmation of the liver disease. However, our patients with elevated liver enzymes were not heavy drinkers, the ratio of AST to ALT was less than 1, and they did not show evidence of viral, metabolic, or autoimmune liver disease, and all them had evidence of fat deposition in the liver by ultrasound. Thus, it is very likely that these patients had NAFLD as the cause of abnormal liver enzymes. Furthermore, although a minimal effect of alcohol cannot be ruled out completely, obesity, but not alcohol drinking, was associated with elevated ALT by logistic regression.

As the present study is a cross-sectional study, we cannot draw any conclusion about a direct relationship between liver dysfunction and obesity. It is now becoming clear that in East Asian populations many subjects with type 2 diabetes with insulin resistance are not obese.[23] And in a preliminary study, workers who gained weight of more than 10% during the past 5 years had a higher ALT level than workers whose body weight remained at nearly the same level during the same period. The above leads to a hypothesis that Asians tend to reveal insulin resistance even with a small increase in body weight.

Other factors, especially genetic factors, may participate in the development of fatty liver, since not all subjects who had gained weight revealed liver dysfunction. We focused on 2 genes that are assumed to be candidates for the development of fatty liver. The β3-AR gene polymorphism has been thought to be related to visceral obesity and insulin resistance.[11-15] Several reports have described a relationship between fatty liver and insulin resistance.[2,24] Therefore, β3-AR gene polymorphism may be involved in the development of fatty liver. We selected the ALDH2 gene as another candidate gene for fatty liver, because the ALDH2 genotype is related to the alcohol drinking habit.[25-27] The present study showed a high prevalence of active ALDH2 among workers with an elevated ALT level. Our results are similar to those of a study that revealed that habitual drinkers with active ALDH2 showed liver dysfunction more often than the subjects with inactive ALDH2.[28] ALDH2 may participate in the metabolism of not only alcohol but also other chemicals with aldehyde radicals, resulting in the alteration of lipid metabolism.

It is interesting to note that the Trp64Arg polymorphism of the β3-AR gene and active ALDH2 were each independently associated with elevated ALT level (Fig 1, β3-AR, $P = .0408$; ALDH2, $P = .0271$, Scheffe's test) among the subjects with normal body weight in the present study. Moreover, all 4 individuals with elevated ALT level and normal BMI had the active ALDH2 genotype and the Arg genotype of β3-AR (Arg genotype means Arg/Arg or Trp/Arg) as shown in Table 6. These results suggest that active ALDH2 and the Arg genotype

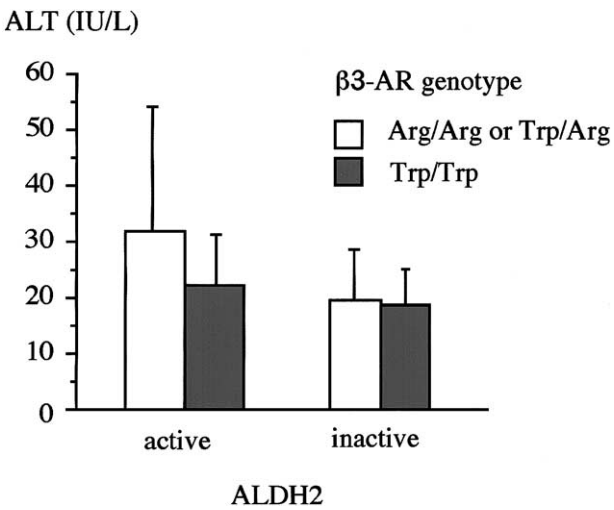

Fig 1. Comparison of the ALT level according to ALDH2 activity and β3-AR polymorphism among workers with normal BMI (19.8 ≤ BMI < 4.2) (n = 80). ALT level was significantly higher among those with active ALDH2 than among those with inactive ALDH2. ALT level was also significantly higher among those with the Arg/Arg or Trp/Arg genotype of β3-AR than among those with the Trp/Trp genotype. (β3-AR, $P = .0390$; ALDH2, $P = .0286$, Scheffe's test).

Table 7. Multiple Regression Analysis With Elevated ALT as the Response Variable

Explanatory Variable	Odds Ratio (95% CI)	*P* Value
BMI	1.564 (1.241-1.991)	<.001
Triglyceride	1.011 (1.004-1.018)	.002
ALDH2 (active)	6.390 (1.031-39.628)	.046

Abbreviation: CI, confidence interval.

of β3-AR are involved in the elevation of ALT level in males by a mechanism other than obesity. Although we did not measure the waist/hip ratio in the present study, visceral obesity in relation to the development of fatty liver in this group should be further investigated.

In conclusion, our study suggests that the genotypes of ALDH2 and β3-AR may be involved in the pathogenesis of abnormal liver enzymes, possibly due to NAFLD. Evaluating ALDH2 and β3-AR genotypes may be useful for predicting and preventing NAFLD as a component of metabolic syndrome.

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