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ORIGINAL ARTICLE **Epidemiology of Allergic Disease**

# Genetic determinants of both ethanol and acetaldehyde metabolism influence alcohol hypersensitivity and drinking behaviour among Scandinavians

**A. Linneberg[1], A. Gonzalez-Quintela[2], C. Vidal[3], T. Jørgensen[1], M. Fenger[4], T. Hansen[5,6], O. Pedersen[5,6,7] and L. L. N. Husemoen[1]**

*[1]Research Centre for Prevention and Health, The Capital Region of Denmark, Glostrup University Hospital, Glostrup, Denmark, [2]Department of Medicine, Complejo Hospitalario Universitario, Santiago de Compostela, Spain, [3]Department of Allergy, Complejo Hospitalario Universitario, Santiago de Compostela, Spain, [4]Department of Clinical Biochemistry, Hvidovre Hospital, Hvidovre, Denmark, [5]Steno Diabetes Center, Gentofte, Denmark, [6]Faculty of Health Sciences, University of Aarhus, Aarhus, Denmark and [7]Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark*

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**Summary**

*Background* Although hypersensitivity reactions following intake of alcoholic drinks are common in Caucasians, the underlying mechanisms and clinical significance are not known. In contrast, in Asians, alcohol-induced asthma and flushing have been shown to be because of a single nucleotide polymorphism (SNP), the acetaldehyde dehydrogenase 2 (ALDH2) 487lys, causing decreased acetaldehyde (the metabolite of ethanol) metabolism and high levels of histamine. However, the ALDH2 487lys is absent in Caucasians.

*Objectives* To investigate the genetic determinants of self-reported alcohol-induced hypersensitivity reactions in Caucasians.

*Methods* The study included two population-based studies of 1216 and 6784 adults living in Copenhagen. Assessment of alcohol consumption and hypersensitivity reactions (in a subgroup) was performed by a questionnaire and was related to common SNPs of genes encoding alcohol dehydrogenases (ADHs) and ALDHs.

*Results* In both populations, alcohol drinkers with a genetically determined fast metabolism of ethanol (the A allele of the ADH1b rs1229984) had an increased risk of alcohol-induced hypersensitivity reactions (odds ratio AA/AG vs. GG in combined populations: 1.82, 95% CI 1.04–3.17). In both populations, a common SNP encoding ALDH1b1 (rs2228093) was found to be significantly associated with alcohol-induced hypersensitivity (odds ratio TT vs. CC in combined populations: 2.53, 95% CI 1.31–4.90).

*Conclusions* Our data support that alcohol sensitivity in Caucasians is genetically determined and suggest that a histamine-releasing effect of acetaldehyde represents a plausible biological mechanism. Furthermore, we present the first report of a clinically significant SNP within the acetaldehyde-metabolizing system in a Caucasian population.

**Keywords** acetaldehyde dehydrogenase, alcohol dehydrogenase, alcohol drinking, respiratory hypersensitivity

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*Correspondence:*
A. Linneberg, Research Centre for Prevention and Health, Glostrup University Hospital, The Capital Region of Denmark, 57 Nrd Ringvej, Building 84/85, DK-2600 Glostrup, Denmark.
E-mail: alli@glo.regionh.dk

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## Introduction

Genetic variations in alcohol metabolism may provide information about individual susceptibility to health effects (both detrimental and beneficial) of alcohol drinking and thus potentially facilitate the development of strategies for personalized prevention. The major enzymes that metabolize alcohol are alcohol dehydrogenases (ADHs) and aldehyde dehydrogenases (ALDHs) (see Fig. 1). In a first step, ethanol is oxidized to acetaldehyde catalysed mainly by the class I ADH isoenzymes (ADH1a, ADH1b and ADH1c). In a second step, acetaldehyde is oxidized to acetic acid catalysed mainly by the mitochondrial ALDH of class II (ALDH2) [1, 2]. Additional ALDHs exist such as the class I ALDH1b, but their role is not known [3]. The ADH1b 47arg as well as the ADH1c 349val and 271gln polymorphisms are associated with the slow metabolism of ethanol and higher alcohol consumption [4]. ALDH2 is

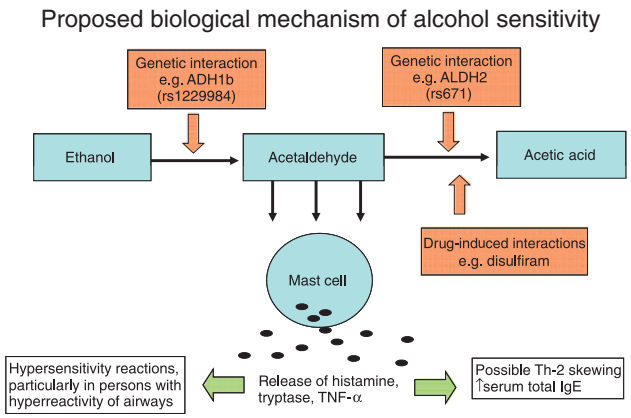


Fig. 1. Proposed biological mechanism of alcohol-induced hypersensitivity reactions and Th2-skewing of the immune system. ADH, alcohol dehydrogenase; ALDH, acetaldehyde dehydrogenase.

also polymorphic and contains an inactive variant (glu487lys) [5, 6]. Carriers of this variant develop high acetaldehyde levels in the blood after drinking ethanol, resulting in alcohol-induced asthma (ALA) and the oriental flushing syndrome. The ALDH2 487gly variant has a strong influence on drinking behaviour such as a strong protective effect against alcoholism [7–10]. Up to 50% of Asians are carriers of the ALDH2 487lys variant [11], which is nearly absent in Caucasian populations [12]. Nevertheless, there are known variations in genes encoding acetaldehyde-metabolizing enzymes in Caucasians, but their function and clinical importance are not known [13–16].

In Asian populations, alcoholic drinks are triggers of hypersensitivity reactions and may result in ALA and the oriental flushing syndrome [17, 18]. The underlying biological mechanisms of ALA have been extensively studied in Asian populations in which ALA affects more than 50–60% of asthmatics [19]. Thus, shortly following alcohol ingestion, a significant increase in serum acetaldehyde occurs, which is paralleled by an increase in blood levels of histamine inducing bronchoconstriction as reflected by a decrease in lung function. Accordingly, inhalation of acetaldehyde itself, but not ethanol, causes bronchoconstriction in human asthmatics [20] and in experimental animal studies [21]. This effect can be completely prevented by pre-treatment with histamine receptor antagonists, supporting that histamine is a key mediator of these reactions [22, 23]. *In vitro* studies of mast cells from human asthmatics [18] and rats [24] show increased release of histamine in response to acetaldehyde, but not to ethanol. Hence, the high prevalence of ALA and flushing in Asians is likely to be attributed to the high prevalence of the inactive ALDH2 487lys variant causing increased levels of acetaldehyde, which in turn induces an increased release of histamine from mast cells [25, 26].

In Caucasian populations, alcoholic drinks are also common triggers of hypersensitivity symptoms from both the upper and the lower airways as well as the skin [27–29]. We have recently reported that 14% of the general adult population in Denmark has experienced hypersensitivity symptoms from the nose, lungs, or skin following intake of alcoholic drinks [30]. These symptoms were more frequent in persons with allergic rhinitis (AR) or asthma. In Caucasian populations, it has been the general belief that these reactions were because of, e.g. intolerance to sulphites or the histamine contents of certain wines. However, there is little evidence to support that these mechanisms play a significant role in the majority of cases of alcohol sensitivity [31–36], although a few cases of IgE-mediated reactions to proteins in wine have been reported [37, 38]. Thus, it may be appropriate to discriminate between reactions specific to wine and reactions to alcoholic drinks in general. We have previously proposed that alcohol-induced hypersensitivity reactions in Caucasians may be caused by a mechanism similar to that described in Asians, i.e. a histamine-releasing effect of acetaldehyde [30].

We present data on the genetic determinants of alcohol hypersensitivity reactions among Caucasians, in which the ALDH2 487lys variant is absent [39]. In two independent Danish populations, we aimed to investigate the effect of various polymorphisms of genes encoding enzymes involved in the metabolism of both ethanol and acetaldehyde on alcohol-drinking behaviour and the risk of alcohol-induced hypersensitivity symptoms.

## Methods

### *The Copenhagen Allergy Study 1998 study population*

The Copenhagen Allergy Study 1998 (CAS98) study was a population-based study performed at the Research Centre for Prevention and Health (RCPH), Glostrup Hospital, between October 1997 and November 1998. The aim of the study was to assess the prevalence and risk factors of allergic diseases. A random sample of 15–69-year-old individuals (born in Denmark and with Danish citizenship) living in 11 municipalities in the South-Western part of the Copenhagen County was drawn from the Civil Registration System and invited to a health examination. A total of 1216 persons (62% of the invited) were examined. The invitation procedure was a two-stage design in order to enrich the study population with persons reporting allergic respiratory symptoms. The first stage included a screening questionnaire survey of allergic respiratory symptoms and the second stage included a health examination, a self-administered questionnaire, and blood drawing. The design and methods of the CAS98 study have been reported in more detail elsewhere [40, 41]. In 2007, a questionnaire on hypersensitivity symptoms induced by alcohol drinking was mailed to all participants. A total of 957 persons completed this questionnaire.

*The Inter99 study population*

The Inter99 study population was used to replicate the results obtained in the CAS98 study population. The Inter99 study was a population-based study performed at the RCPH in the same background population as the CAS98 study. The study design has been described previously in more detail [42]. A random sample of 30–60-year-olds living in 11 municipalities (the same as above) in the South-Western part of the Copenhagen County were invited for a health examination including a screening for cardiovascular risk factors. Thus, between 1999 and 2001, a total of 6784 individuals (52.5% of the invited) participated in the health examination and completed a questionnaire on lifestyle, health, and socioeconomic factors. All participants in the Inter99 study were invited for a five-year follow-up (a total of 4513 individuals participated), which was completed in April 2006 [43]. A total of 2419 consecutive participants in the follow-up completed an additional questionnaire about alcohol hypersensitivity symptoms. Participants of non-Scandinavian and Finnish origin were excluded from the data analyses ($n = 270$).

*Assessment of alcohol hypersensitivity and allergic rhinitis*

In both populations, alcohol hypersensitivity was assessed using the same questions. These questions have previously been used for the assessment of alcohol hypersensitivity in a general population survey [30]. Alcohol hypersensitivity was defined as a positive answer to at least one of the following three questions:

(1) 'Have you ever experienced itchy nose, sneezing, runny nose, or stuffy nose following intake of alcoholic drinks?'
(2) 'Have you ever experienced wheezing or whistling in your chest, breathlessness, or coughing, following intake of alcoholic drinks?'
(3) 'Have you ever experienced symptoms from the skin such as a rash, itching or swelling of the skin, following intake of alcoholic drinks?'

In both populations, 'putative AR' was defined as an affirmative question to least one of two questions:

(1) 'Have you had an itchy or stuffy nose or have you been sneezing when near grass, trees, or flowers?'
(2) 'Have you had an itchy or stuffy nose or have you been sneezing following exposure to furry animals, e.g. horse, dog, cat, rabbit, guinea-pig, or hamster?'

*Assessment of alcohol drinking*

In both studies, information on alcohol drinking was obtained from the self-administered questionnaire using the same questions. The on average amount and type (beer, wine, dessert wine, spirits) of alcoholic beverage consumed per week in the last 12 months were recorded. A standard drink was defined as 1.5 cL or 12 g of pure ethanol. Thus, one beer, one glass of wine, or one glass of spirit was considered as one standard drink. The total weekly alcohol intake was calculated as the sum of weekly intakes of beer, wine, dessert wine, and spirits. The total weekly alcohol intake as assessed by this method in another population-based study has previously been found to be positively associated with increased levels of serum γ-glutamyl transferase (GGT), a marker of high alcohol intake [44]. Excessive drinking was defined as alcohol consumption above the recommendations of the Danish National Board of Health (women $> 14$ standard drinks per week and men $> 21$ standard drinks per week).

*Genotyping of alcohol and aldehyde dehydrogenase polymorphisms*

In the CAS98 study, the *ADH* and *ALDH* variants were identified by TaqMan Chemistry (Applied Biosystem, Nieuwerkerk a/d IJssel, the Netherlands) or PCR amplification, followed by restriction cleavage analysis. The following single nucleotide polymorphisms (SNPs) were examined: ADH1b arg47his (rs1229984), ADH1c ile349-val (rs698), ADH1c arg271gln (rs1693482), ALDH2 glu487lys (rs671) [5, 6], ALDH2 5′-UTR A-357G (rs886205) [13, 14], ALDH1b1 ala69val (rs2228093) [15, 16], and ALDH1b1 arg90leu (rs2073478) [15, 16]. The ALDH2 glu487lys (rs671) variant was genotyped only in the CAS98 population, in which only one person was found to be heterozygous for the mutation (none was homozygous). In the CAS98 study population, the two ADH1c variants (rs698 and rs1693482) were in complete linkage disequilibrium and we only chose to genotype one of them (rs1693482) in the Inter99 study population. Thus, in the Inter99 study, five of the above SNPs (rs1229984, rs698, rs886205, rs2228093, rs2073478) were genotyped by TaqMan allelic discrimination (KBiosciences, Hoddesdon, UK). All genotyping success rates were above 96.6%, with a mismatch rate below 0.26% in 384 duplicate samples.

*Ethics.* Both the CAS98 study (KA 97050) and the Inter99 study (KA 98 155) both approved by the Ethics Committee of Copenhagen County. The present analyses including genotyping were part of a protocol, which was approved as an independent project by the Ethics Committee of Copenhagen County (KA 02136).

*Statistical analyses*

Statistics were computed with the statistical program SAS version 9.1 (SAS Institute Inc, Cary, NC, USA). All *P*-values are two-tailed and statistical significance was

defined as $P<0.05$. In this paper, we present data analyses performed on the combined study populations. Deviations from the Hardy–Weinberg equilibrium were tested by $\chi^2$ analyses with 1 degree of freedom.

The associations of ADH and ALDH gene variants with alcohol drinking habits and alcohol hypersensitivity were examined by means and medians (continuous data) and in simple frequency tables (categorical data), and differences were tested by the Wilcoxon two-sample test/the Kruskal–Wallis test (continuous data), or the Cochran–Armitage trend test (categorical data). The Cochran–Armitage test for genetic association is robust to Hardy–Weinberg disequilibrium.

The risks (odds ratios) of alcohol hypersensitivity associated with the ADH1b (rs1229984) and ALDH1b1 (rs2228093) gene variants were estimated in logistic regression models including pooled data from both the inter99 and the CAS98 study populations. The likelihood ratio test and Wald's test for single parameters were used to test for statistical significance. Models were adjusted for sex, age, weekly alcohol intake, study population (Inter99 vs. CAS98), and the two gene variants mentioned above. Linear trends across ordered genotype categories were tested by scoring the categories and modelling the variables as continuous variables in the models. In addition, interaction effects of ADH1b (rs1229984) and ALDH1b1 (rs2228093) gene variants with alcohol drinking were estimated and evaluated by including the relevant interaction terms in the regression models. Similarly, it was tested whether the effects of these SNPs differed between the two populations by testing for interaction between the SNP and the study population (Inter99 vs. CAS98). Persons with missing values on the various variables were excluded where relevant. Thus, $N_{total}$ may differ in the various analyses. In the analyses of associations between alcohol genotypes and alcohol hypersensitivity, only those who answered the additional questionnaire on alcohol hypersensitivity were included.

## Results

### *Alcohol genotypes and alcohol drinking behaviour*

Table 1 shows the distribution of genotypes in the combined study populations. The ADH1b (rs1229984) SNP

**Table 1.** Association of polymorphisms of alcohol dehydrogenase (ADH) and acetaldehyde dehydrogenase (ALDH) with alcohol drinking habits

| Genotype | *n* (%) | Drinks per week* | Non drinking % (*n*/total *n*)†,‡ | Excessive drinking >14 (♀); >21 (♀) % (*n*/total *n*)†,‡ |
|---|---|---|---|---|
| ADH1b (rs1229984) | | | | |
| GG, slow | 6995 (96.23)¶ | 9.90 (6) | 10.65 (721/6770) | 15.14 (1025/6770) |
| GA, intermediate | 263 (3.62) | 7.74 (4) | 17.15 (41/239) | 10.88 (26/239) |
| AA, fast | 11 (0.15) | 3.33 (3) | 44.44 (4/9) | 0 (0/9) |
| | | $P<0.001$ | $P<0.001$ | $P=0.032$ |
| ADH1c (rs1693482) | | | | |
| CC, fast | 2446 (33.79) | 9.14 (6) | 10.61 (249/2347) | 13.29 (312/2347) |
| CT, intermediate | 3529 (48.76) | 9.94 (6) | 11.50 (393/3417) | 15.19 (519/3417) |
| TT, slow | 1263 (17.45) | 10.62 (6.5) | 10.24 (125/1221) | 17.44 (213/1221) |
| | | $P=0.060$ | $P=0.984$ | $P<0.001$ |
| ALDH2 (rs886205) | | | | |
| TT | 4928 (68.17) | 9.84 (6) | 10.51 (502/4778) | 15.03 (718/4778) |
| CT | 2103 (29.09) | 9.72 (6) | 11.81 (237/2006) | 14.76 (296/2006) |
| CC | 198 (2.74) | 9.48 (6) | 12.31 (24/195) | 14.87 (29/195) |
| | | $P=0.519$ | $P=0.096$ | $P=0.796$ |
| ALDH1b1 (rs2228093) | | | | |
| CC | 5593 (76.89) | 9.66 (6) | 11.24 (607/5402) | 14.79 (799/5402) |
| CT | 1563 (21.49) | 10.32 (6.5) | 9.45 (142/1503) | 15.37 (231/1503) |
| TT | 118 (1.62) | 11.14 (7.5) | 11.30 (13/115) | 20.00 (23/115) |
| | | $P=0.006$ | $P=0.099$ | $P=0.223$ |
| ALDH1b1 (rs2073478) | | | | |
| TT | 2620 (36.16) | 9.58 (6) | 11.06 (280/2531) | 14.50 (267/2531) |
| GT | 3491 (48.18) | 9.75 (6) | 10.79 (363/3365) | 14.71 (495/3365) |
| GG | 1134 (15.65) | 10.35 (6) | 11.39 (125/1097) | 16.41 (180/1097) |
| | | $P=0.643$ | $P=0.890$ | $P=0.195$ |

*Mean (median) standard drinks (one standard drink corresponds to 1.5 cL/12 g pure ethanol). *P*-values were obtained by the Wilcoxon two-sample test/Kruskal–Wallis test.

†*P*-values were obtained by the Cochran–Armitage trend test.

‡Proportion of non (or excessive) drinking persons among those with the specific genotype.

¶Statistically significant deviation from the Hardy–Weinberg equilibrium ($P<0.001$).

deviated from Hardy–Weinberg equilibrium in the Inter99 study population, while the ALDH1b (rs2228093) SNP deviated from Hardy–Weinberg equilibrium in the CAS98 study population. Table 1 also shows the association of ADH and ALDH genotypes with alcohol drinking behaviour. The previously reported association of the ADH1b (rs1229984) G allele and the ADH1c (rs1693482) T allele with increased alcohol intake was confirmed [45]. A significant association of the ALDH1b (rs2228093) variant with alcohol drinking was observed in both populations, the T-allele showing a significant association with increased intake of alcoholic drinks, but not a significant association with excessive drinking. None of the other SNPs were associated with alcohol drinking.

### *Alcohol genotypes and alcohol hypersensitivity*

As shown in Table 2, both the ADH1b (rs1229984) A allele and the ALDH1b (rs2228093) T allele were associated with alcohol hypersensitivity in the combined Inter99 and CAS98 study populations (non-drinkers excluded). These associations were present in both populations, although the ADH1b polymorphism did not reach statistical significance in the smaller CAS98 population, in which no mutant homozygous participants were found (data not shown). Accordingly, the ADH1c (rs1693482) C allele also tended to be associated with a higher prevalence of alcohol hypersensitivity, but this was not statistically significant. Logistic regression models (with alcohol hypersensitivity as the dependent variable) including both the ADH1b (rs12299884) and the ALDH1b (rs2228093) genotypes in the same model (including participants from both study populations) showed that the effects of the two polymorphisms were independent of each other, both having a statistically significant effect on the risk of alcohol hypersensitivity (see Table 3). This effect was stronger in alcohol drinkers and not evident in non-drinkers (see Table 3). In the regression model with both drinkers and non-drinkers, none of the tested gene-by-alcohol interactions were found to be statistically significant, although the interaction between the effect of ADH1b (rs1229984) SNP and alcohol consumption on the risk of alcohol hypersensitivity was borderline statistically significant ($P = 0.07$ in the unadjusted model and $P = 0.11$ in the fully adjusted model). Thus, none of these interactions were found to be significant from a statistical point of view when investigated in the multiplicative logistic regression model. Adding smoking status to these models did not change the estimates for the effects of the SNPs. Smoking status in itself was not significantly associated with the prevalence of alcohol-induced hypersensitivity reactions. The relatively low number of excessive drinkers might not have allowed us to fully take into account the potential confounding effects of smoking. In a similar model, we tested for interactions between these SNPs and the study population (Inter99 vs. CAS98), but none of these interaction terms were found to be statistically significant ($P > 0.60$). Thus, the effects of the SNPs on the prevalence of alcohol-induced hypersensitivity reactions can be assumed to be similar in the two study populations, supporting that it is reasonable to merge the two populations in the analyses. Finally, we tested for an interaction between the two SNPs and 'putative AR'. None of the interactions between 'putative AR' and genotype were found to be statistically significant ($P > 0.29$).

**Table 2.** Association of polymorphisms of alcohol dehydrogenase (ADH) and acetaldehyde dehydrogenase (ALDH) with the prevalence of alcohol-induced hypersensitivity reactions (non-drinkers excluded)

| | Prevalence of hypersensitivity reactions (%, $n/n_{total}$) |
|---|---|
| ADH1b (rs1229984) | |
| GG, slow | 15.32 (398/2598) |
| GA, intermediate | 23.61 (17/72) |
| AA, fast | 50.00 (1/2) |
| | $P = 0.025$ |
| ADH1c (rs1693482) | |
| CC, fast | 16.09 (140/870) |
| CT, intermediate | 16.57 (218/1316) |
| TT, slow | 12.53 (59/471) |
| | $P = 0.158$ |
| ALDH2 (rs886205) | |
| TT | 15.97 (291/1822) |
| CT | 14.83 (113/762) |
| CC | 12.66 (10/79) |
| | $P = 0.316$ |
| ALDH1b1 (rs2228093) | |
| CC | 14.52 (298/2052) |
| CT | 18.56 (108/582) |
| TT | 31.11 (14/45) |
| | $P < 0.001$ |
| ALDH1b1 (rs2073478) | |
| TT | 15.29 (125/994) |
| GT | 16.16 (203/1256) |
| GG | 15.95 (67/420) |
| | $P = 0.662$ |

*P*-values represent result of Cochran–Armitage trend test.

## Discussion

We found that genetic variations in both the ethanol- and the acetaldehyde-metabolizing systems determine the risk of alcohol hypersensitivity as well as alcohol drinking among Scandinavians. This raises the hypothesis that interactions between alcohol drinking and genetic variation in acetaldehyde metabolism, which is clinically important in Asians, also play a role in Caucasians and determine their susceptibility to the effects of alcohol drinking on the immune system.

In line with our results, Macgregor et al. [46] found that the ADH1b (rs12229984) A allele was significantly

**Table 3.** Relative risk of alcohol-induced hypersensitivity reactions associated with two polymorphisms of alcohol dehydrogenase 1b (ADH1b) and acetaldehyde dehydrogenase 1b1 (ALDH1b1) stratified by alcohol-drinking status (non-drinkers and drinkers) in the combined Inter99 and CAS98 study populations

| | Odds ratio (95% CI)* | | All participants |
|---|---|---|---|
| Genotype | Drinkers | Non-drinkers | Odds ratio (95% CI)† |
| ADH1b (rs1229984) | | | |
| GG, slow | 1 (reference) | 1 (reference) | 1 (reference) |
| GA/AA, intermediate/fast | 1.82 (1.04–3.17) | 0.42 (0.05–3.26) | 1.55 (0.91–2.64) |
| | $P = 0.022$ | $P = 0.404$ | $P = 0.117$ |
| ALDH1b1 (rs2228093) | | | |
| CC | 1 (reference) | 1 (reference) | 1 (reference) |
| CT | 1.34 (1.04–1.71) | 0.97 (0.42–2.22) | 1.30 (1.03–1.65) |
| TT | 2.53 (1.31–4.90) | 1.11 (0.12–10.40) | 2.36 (1.26–4.43) |
| | $P$ for trend = 0.001 | $P$ for trend = 0.990 | $P$ for trend = 0.002 |

*Odds ratios obtained in a logistic regression model including sex, age, study population (Inter99 vs. CAS98), and genotypes shown in the table.
†Odds ratios obtained in a logistic regression model including sex, age, alcohol consumption (continuous), study population (Inter99 vs. CAS98), and genotypes shown in the table. *P*-values for interactions in this model: $P = 0.110$ [alcohol (drinking vs. non-drinking)×ADH1b (rs1229984)] and $P = 0.603$ [alcohol (drinking vs. non-drinking)×ALDH1b1 (rs2228093)].

associated with 'negative reactions' such as flushing, nausea, palpitations, etc., following alcohol intake. They did not observe any associations between such reactions and ALDH2 gene variation. They did not, however, investigate the role of ALDH1b gene variation. Our finding that the common ALDH1b (rs2228093) T allele was associated with alcohol drinking and alcohol hypersensitivity (observed in two independent populations) is novel. We examined five SNPs, and this novel association could be a type I error. However, the *P*-value would still be less than 5% after correction for multiple testing, e.g. the Bonferroni method. To our knowledge, this is the first study to report a clinically significant polymorphism within the acetaldehyde-metabolizing system among Caucasians. The function of the ALDH1b1 (rs2228093) SNP is not known.

The finding that carriers of the fast-metabolizing ADH1b (rs12229984) A allele (who experience higher peak levels of acetaldehyde following intake of alcoholic drinks) have a higher risk of alcohol hypersensitivity when drinking alcohol supports the hypothesis that acetaldehyde (and not ethanol) is the substance responsible for hypersensitivity reactions induced by alcoholic drinks. Thus, our data support the idea that acetaldehyde, consistent with what has been shown in Asians, can trigger hypersensitivity reactions in Caucasians. Accordingly, we propose that a histamine-releasing effect of acetaldehyde, as has been demonstrated in Asians, also represents a plausible biological mechanism for these reactions among Caucasians (see Fig. 1).

There is strong evidence that the prevalence of allergic disease has increased world-wide and this increase appears to be linked to adoption of a Westernized, affluent, and urbanized lifestyle. The specific factors responsible for this increase are not known. There is strong evidence that alcohol influences the immune system in several ways, e.g. alcohol impairs the T-helper 1 lymphocyte regulated cell-mediated immune response, leading to increased susceptibility to bacterial infections [47, 48], increases serum total IgE [47, 49], and skews the immune response towards Th2 [50]. Little is known about the influence of alcohol on the allergen-specific IgE immune response, although a few studies have linked alcohol consumption to IgE sensitization against inhalant allergens [44, 51, 52] and incidence of self-reported perennial AR [53]. Furthermore, alcohol consumption during pregnancy has been linked to early atopic markers (cord blood total IgE and early onset atopic dermatitis) in the offspring, suggesting that alcohol influences the fetal immune system [54, 55]. Hence, our finding that alcohol-induced hypersensitivity in Caucasians is genetically determined and likely to be induced by a mechanism similar to that underlying ALA and flushing in Asians may suggest that alcohol should be considered as a potential clinically relevant trigger and aggravating factor of atopic manifestations in Caucasian populations. However, more studies of the immunological effects of alcohol seem warranted.

Furthermore, it would be of interest to investigate whether there may be differences between the mechanisms underlying reactions specific to wine and reactions to alcohol in general.

The ADH1b (rs1229984) SNP deviated from Hardy–Weinberg equilibrium. This may be because of the possibility that the study populations might have included a few persons of other ethnic origins (population stratification). This explanation seems plausible, because this allele shows large variations in frequency between populations even within Europe [56].

## Conclusions

In this Scandinavian general population, we found that persons with a genetically determined fast metabolism of ethanol were at an increased risk of alcohol-induced hypersensitivity reactions, supporting the hypothesis that acetaldehyde may be the substance underlying these reactions (see Fig. 1). Finally, this is the first report on a clinically significant SNP (ALDH1b) of a gene within the acetaldehyde-metabolizing systems among Caucasians. More investigations into the mechanisms underlying the effect of alcohol on the immune system seem warranted, e.g. ADH/ALDH-gene-targeted animal studies and *in vitro* studies.

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